PEDIATRIC CLINICS OF NORTH AMERICA

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MADE IN THE UNITED STATES OF AMERICA AT THE PRESS OF W. B. SAUNDERS COMPANY

The Pediatric Clinics of North America is published quarterly by
W. B. Saunders Company, West Washington Square, Philadelphia 5, Pennsylvania.
Subscription price is $15.00 per year. Entered as second-class matter, June 10, 1958, at the Post Office, Camden, New Jersey, under the Act of March 3, 1879. Second-class postage paid at Camden, New Jersey.

This issue is Volume 8, Number 3

Library of Congress Catalog Card Number: 54–6097

August, 1961

Symposium on Pediatric Dermatology

Carroll F. Burgoon, Jr., M.D.
Consulting Editor

Volume 8, Number 3

W. B. Saunders Company

Philadelphia & London

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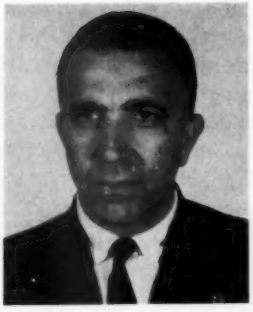
FOREWORD

CARROLL F. BURGOON, JR., M.D.

Consulting Editor



The last dermatologic number of the *Pediatric Clinics*, in 1956, was undertaken by the consulting editor because of the expressed desire of physicians for an up-to-date, concise survey of some of the diseases of the skin commonly seen in infants and children. Before the publication of the Symposium on Pediatric Dermatology and the two recent textbooks on Pediatric Dermatology, the physician was completely lost if he tried to look for information on skin diseases in the pediatric age group. For the most part the child was completely ignored or lost in the consideration of the cutaneous system.

It is difficult to understand how so important an organ has been so completely bypassed by both the pediatrician and the dermatologist. The exception to this statement has been the interest in function of the eccrine sweat glands in pancreatic cystic fibrosis which was stimulated by Di Sant' Agenese's observations.

Basic knowledge of the structure and function of the skin of the newborn and the infant is so sketchy as to be nonexistent for practical purposes. The alteration in function which occurs in the skin and dermal appendages at the time of birth, and the mechanism of the defluvium which occurs at 8 and 10 weeks are unknown. Even the origin and function of the vernix caseosa are disputed, and there are conflicting opinions to whether its presence is normal or abnormal.

Clinical observation would suggest that the child's cutaneous system is not just a miniature of the adult system, e.g., the propensity of the

neonatal skin to respond with blister formation to inflammation, the puberal resident "flora" of the skin in comparison to adult skin, and the invasion of the prepuberal child's scalp by dermatophytes, to mention only a few differences.

Most dermatologists are not fully aware of the different response of the infant's and child's skin as compared to that of the adult, because of the lack of opportunity to observe and treat children during their training period. There is a hiatus not only in the dermatologist's education, but also in that of the pediatrician, who usually completes his education with little more than a smattering of knowledge of the cutaneous system. In an effort to bridge the gap, our department has been offering a one-year educational program for pediatricians and presenting a yearly postgraduate course in Pediatric Dermatology for the practicing physician who is particularly interested in the child.

It would seem worth while to review some of the more interesting recent advances in pediatric dermatology for the busy physician who is interested in the care of the child. Because of departmental interest in the child's skin, many of the articles in this symposium are written by members of our department, while others were selected because of a special interest and knowledge of the child's cutaneous system. I am indebted to the members of the Department who helped in preparing the papers and proofreading the papers, especially to J. S. Burgoon, Frederick Urbach, James Graham and Edward DeLamater; to my secretaries, Nancy Gordon and Ronalda Kapczynski for the preparation of the manuscripts; to Jane Kent for the preparation of the graphs; and to Gerald Pearlman, our departmental medical photographer.

GENETICS OF SOME PEDIATRIC DERMATOLOGIC SYNDROMES

EDWARD D. DE LAMATER, M.D.

Since the establishment by Garrod[6, 7] of the reality of hereditary metabolic disorders in human disease, and the subsequent development of the one-gene-one-enzyme hypothesis by Beadle and Tatum,[2] and its extension and elaboration by their respective associates and students (Strauss[17]), success has been achieved in the direct practical application of these ideas to the problems of human disease.[9] There is hope for the ultimate understanding of many such problems. The evolution, at least in individual cases, of the development of methods of therapy by substitution for the defect produced by the enzyme malfunction (or lack) or by the limitation of ingestion of toxic substrates has been demonstrated as feasible and possible.

Demonstration by Watson and Crick[18, 19] of the likely organization of the genic material, deoxyribosenucleic acid (DNA), and the genetic implications of this highly organized macromolecule as the carrier of a code in the sequence of its purine and pyrimidine basis, constitute a fundamental advance. When these concepts are combined with the studies of the amino acid sequences of such abnormal proteins as occur in sickle cell anemia[8] and to such sequences in active enzymes,[1] an ultimate insight into the mechanism of hereditary control at the molecular and metabolic levels is conceived of as approachable. Presumably all proteins, including enzymes, are synthesized under the control of specific codes in the deoxyribosenucleic acid, so that modification of this code, as in a gene mutation, would be reflected in a modified and, therefore, abnormal protein.

Since, so far as we know, all biochemical reactions are dependent upon organic catalysts, i.e. enzymes, which are proteinaceous, it is implied that genetic blocks act through modification of such proteinaceous catalysts.

A brief consideration of the mechanism of genetic blocks should perhaps be given. Treatment of this subject has been presented in detail by McKusick[11] and Dent.[4] Simply stated, the problem is as follows. Let us suppose that the normal metabolism of a substance A is changed successively by separate specific enzymes to substances B, C, and D. If D is the final excretory product, such as urea, then it is likely to be found in some organ in large quantities; but the preceding compounds B and C, depending on their rates of turnover, need be present in minute or even undetectable amounts. If, however, a genetic defect occurs in which the enzyme for turning C into D is partly or completely absent (or for some reason inactive), two consequences could ensue: (1) accumulation of substance C in large amounts, and (2) an absence or reduced amount of the well known metabolite substance D. In certain favorable situations it may be possible to detect the absence or reduced activity of the enzyme by direct methods, but such a gross demonstration of the absence or defective function of an enzyme may not be possible for diverse biochemical reasons which are clearer today than in Garrod's time, and we are enforced to invoke further concepts to elucidate these more complex situations. This will be seen in a simple example in which a normal urinary constituent may accumulate in the body; the mechanism of its transport through the kidney to the urine is blocked by a defect in the necessary enzyme for its transport. Permutations of this general type of defect are obvious.

Extensive studies of various human and animal diseases are proceeding in numerous efforts to define the nature of the metabolic and biochemical deficiencies in a number of disorders.[3, 5] Such deficiencies by inference, as indicated above, reflect some modification in enzyme structure. Unfortunately, at present relatively few of these studies relate directly to the skin or cutaneous diseases, and particularly those cutaneous diseases of childhood. Several of the hereditary metabolic diseases currently under study do, however, have cutaneous manifestations, some of which become apparent in childhood. A brief survey of these will be presented along with an indication of the current status of each. In addition, several other important cutaneous diseases of established hereditary origin, about which little of the biochemical deficiencies or mechanisms is known, will be considered, but more briefly from the clinical and genetic points of view. No effort will be made here to present an exhaustive treatment of this complex subject. Extensive reference for this review has been made to Dent,[5] Childs and Sidbury[3] and Sorsby.[16]

METABOLIC DISEASES WITH CUTANEOUS MANIFESTATIONS

ALKAPTONURIA

CLINICAL. Alkaptonuria is a congenital disorder of the intermediary protein metabolism, and in particular it is a disorder of phenylalanine and tyrosine metabolism (Fig. 1). Transformation of these aromatic amino acids is interrupted at the stage of homogentisic acid, which is eliminated in the urine and may be detected by a darkening of the urine when exposed to air or by the addition of alkali. It is frequently recognized in infants by the staining it produces in the diaper. There is a greenish-brown coloration of the sebum secretion, primarily in the axilla, and of the cerumen. The cartilage of the nose and ears may show a brownish-blue pigmentation (ochronosis), and blue spots may also appear on the sclera, the conjunctiva, the cheeks, the gums, and even on the nails and the thenar and hypothenar eminences. Histo-

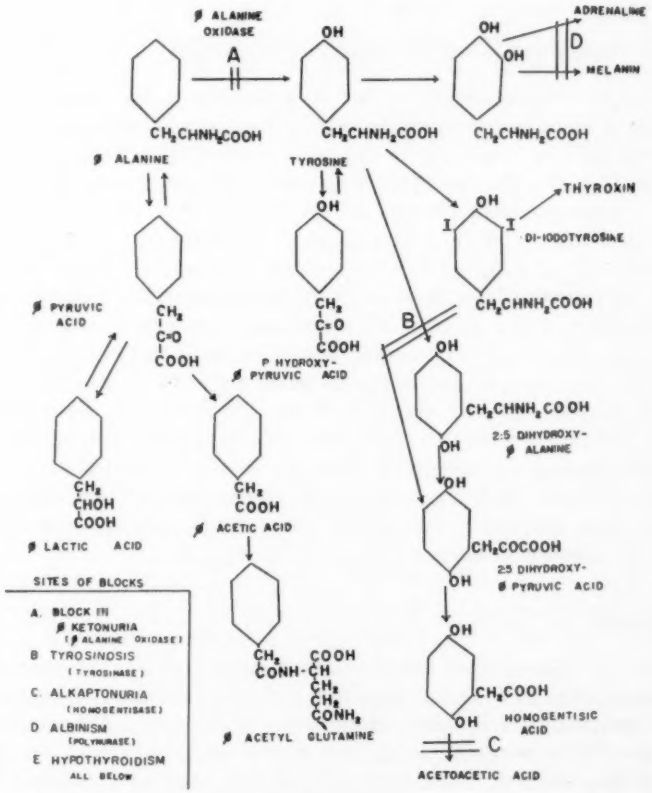


Fig. 1.

pathologic study has revealed ochronosis in the trachea, the vascular intima and the endocardium. Degenerative osteoarthritic lesions, which primarily affect the vertebral column and the large joints, occur around 40 years of age, owing to the deposition of homogentisic acid in the articular cartilage.

Clinical diagnosis is based on the recognition of the reducing properties of homogentisic acid in the urine, which reduces Fehling's and Benedict's solutions, but gives negative results with Nylander reagent. Fermentation tests and the polariscope distinguish it from diabetes.

HEREDITARY. Garrod[7] recognized the familial occurrence of this disease and the high frequency of consanguineous marriages among the parents of the affected children. These observations were interpreted as indicating a recessive mode of transmission. The concept of a single recessive mendelian factor has subsequently been confirmed on numerous occasions. Nevertheless, cases of alkaptonuria with dominant genetic transmission have also been recognized.

PHENYLKETONURIA (PHENYLPYRUVIC OLIOGOPHRENIA)

CLINICAL. This disorder consists in a failure of the transformation of phenylalanine into tyrosine, and is the second hereditary disorder considered here occurring in the same metabolic pathway as alkaptonuria (Fig. 1). In consequence of the block between phenylalanine and tyrosine, persons affected show a tendency to a lack of pigmentation and concomitantly a hypersensitivity to sunlight. They also show a tendency to hyperhidrosis, and eczematous affections are frequent. The disturbance is present from birth and is characterized by the elimination in the urine of phenylpyruvic acid, which is never found in normal persons. The ferric chloride test for phenylpyruvic acid produces a deep green color. In about 60 per cent of cases the mental level is about that of idiocy, and about 30 per cent are imbeciles. Epileptiform seizures are frequent. The biochemical basis for the psychoneurologic syndrome is obscure.

HEREDITARY. As with alkaptonuria, consanguineous marriages occur with high frequency among the parents of patients, suggesting a simple recessive inheritance.

ALBINISM

CLINICAL. Generalized albinism is characterized by the absence of pigment, especially in the skin, hair and eyes. The lack of pigment in the eyes is associated with a diminution of vision, which is not merely due to the absence of the pigment, but is related also to a hypoplasia or aplasia of the fovea centralis. The lack of pigment is due to a block

in the oxidizing enzyme, tyrosinase (dopa-oxidase). This enzyme likewise occurs in the same metabolic system as the two previously discussed, and results in a complete inhibition in the process of pigmentation. Albinism is often associated or combined with other anomalies, particularly deaf-mutism, oligophrenia, epilepsy and polydactylia.

HEREDITARY. Albinism is most frequently transmitted as a recessive trait, but may rarely occur as a dominant. The frequency of this anomaly in the population is estimated at one in every 20,000.

AMYLOIDOSIS

CLINICAL. Generalized amyloidosis (Lubarsch-Pick) is a disturbance of protein metabolism characterized by deposits of a pathologic albuminoid in the vascular walls and the pericapillary tissues of the liver, spleen, kidneys, adrenal, intestine, testicle and, on occasion, the tongue. In the skin it produces a scleroderma-like response and amyloid tumors. An amyloidosis which affects only the skin has been described. This condition, suspected on clinical grounds, is recognized by the removal of congo red from the circulation, owing to the absorption of this dye by the amyloid. Histopathologically, the amyloid is recognized as a vitreous, translucent substance which is stained brown by iodine solutions.

HEREDITARY. A dominant inheritance has been suggested.

GAUCHER'S DISEASE

CLINICAL. Gaucher's disease is characterized by the storage of cerebrosides in reticular cells and histiocytes of the spleen, liver, lymph nodes and bone marrow. Clinically, two forms can be distinguished: (1) a chronic benign form which begins after infancy and evolves slowly, and (2) an acute, malignant form which begins early in infancy and progresses rapidly.

In the chronic form there is a pronounced splenomegaly with a less pronounced hepatomegaly, with a bronze pigmentation of the skin, particularly in those areas exposed to light, and a brownish thickening of the bulbar conjunctiva at the angles of the eyes. Lesions of the skeletal system, and also a secondary hypochromic anemia, leukopenia and thrombopenia are prominent. Biopsy of the long bones reveals voluminous cells with eccentric nuclei and a reticular or fibrillar protoplasm containing vacuoles and infiltrated by kerasin.

The acute form of the disease is evident by the fifth or sixth month of life, and is characterized by a voluminous spleen and prominent neurologic signs with physical and mental retardation. This syndrome of "progressive cerebral decortication" ends in cachexia and death.

HEREDITARY. A recessive mode of inheritance has been observed; however, the condition appears to be transmitted also as a dominant. There is no sex predilection. The disease is frequently familial, and a high frequency of stillbirths and abortions occurs in these families.

It has been suggested that there is a relation between Tay-Sachs disease (amaurotic idiocy) and Gaucher's disease.

NIEMANN-PICK DISEASE

CLINICAL. Niemann-Pick disease closely resembles the infantile form of Gaucher's disease, but runs a more rapid course to a fatal issue before the end of the second year. Unlike Gaucher's disease, the affection is not limited solely to the reticuloendothelial system, but invades both the parenchymal and mesenchymal elements of the affected organs. The characteristic substance of Niemann-Pick disease is a lipid complex composed primarily of phosphatides (sphingomyelin). The disease is rare and shows a predilection for the female sex and for the Jewish race. Clinically, there are feeding difficulties, hepatosplenomegaly, brownish-yellow discoloration of the skin, and enlargement of the lymph nodes. Hypercholesterolemia and modifications of the blood concentrations of different lipoid substances occur. Neurologic signs and mental deficiency with opisthotonos, convulsions and spastic paraplegia occur, and in about one third of the cases a cherry-red spot surrounded by a white zone is observed in the macular region. Some neurologists consider Niemann-Pick disease and Tay-Sachs disease to be identical. The differences in the stored substance (sphingomyelin) may ultimately demonstrate that these two diseases are distinct, however, in the same general manner it has been found that von Gierke's disease actually includes several closely related biochemical disorders. Thus clinically comparable diseases included under the same present heading may actually constitute discrete hereditary disease entities, when more becomes known of the specific biochemical defects.

HEREDITARY. The disease occurs within families and has been demonstrated to have concordant appearance in identical twins, although consanguinity among parents of affected persons has not been observed. Recessive transmission is generally assumed.[13] Pfändler considers the disease to have regular dominant inheritance with low penetrance.

HAND-SCHÜLLER-CHRISTIAN DISEASE (CRANIOHYPOPHYSIAL XANTHOMATOSIS)

CLINICAL. The clinical aspects include, classically, cranial lacunae, exophthalmos and diabetes insipidus, occurring in late infancy. There

are also growth disturbances, apathy, polydipsia and polyuria. Secondary symptoms include intracranial hypertension, hypogenitalism, deafness, neurologic disturbances and ocular disorders. Xanthomatous eruptions of the skin, eyelids, conjunctivae, corneal limbus, and a corneal lipoid dystrophy have been observed. The liver, spleen, lymph nodes, lungs and other organs may be affected, and bone lesions other than those of the cranium may occur. Hypercholesterolemia is present in about half of the cases. Biopsy of affected tissue demonstrates the characteristic xanthomatous cells with double refractile lipoids. The exact nature of the metabolic disturbance has not been identified.

HEREDITARY. The disease occurs in fraternal twins, and familial cases have been reported. Presumably it is a rare recessive trait.

THE PRIMARY XANTHOMATOSES

CLINICAL. There are five general groupings, according to the area of deposition of the fatty substances: (1) tuberous xanthomatosis of the skin (xanthoma tuberosum); (2) xanthomatosis of the tendon and tendon sheaths; (3) cardiovascular xanthomatosis; (4) xanthomatosis of the bile ducts; (5) xanthomatosis of the spleen, liver and lymph nodes. The disease usually appears in the thirties or later, but may rarely occur in late childhood or the teens.

All possible combinations and transitions may exist between these forms. Tuberous xanthomatosis is characterized by the appearance of yellow-brownish nodules or tumors on the extensor surfaces (elbows, knees, heels, and elsewhere), and often involving the eyelids (xanthelasmas).

HEREDITARY. This disease has a familial and hereditary tendency. It appears to be transmitted as a dominant, which may be irregular. A high frequency of elevated blood cholesterol among relatives of patients suggests simple dominance with low penetrance. It may be that the hypercholesterolemia represents the heterozygous state, and the tuberous xanthomatosis the homozygous state, and that the genetic pattern is in reality a recessive one.

LIPOIDOSIS OF THE SKIN AND MUCOUS MEMBRANES (LIPID PROTEINOSIS)

CLINICAL. This disease is characterized by nodular or hyperkeratotic lesions distributed over the face, scalp, neck and extremities. The mucous membranes of the lips, frenulum linguae, palate, pharynx and larynx show yellow-white patches consisting of lipoid deposits. In the child the affection causes a raucous voice or an aphonia. Laryngeal stenosis may require tracheotomy. Cicatrization of the varioliform eruptions can produce a pockmarked appearance. Blood and

skin phosphatide lipoids may be increased. Latent diabetes may accompany the disorder.

Histologically, lipoid deposits surround the capillaries and infiltrate the neighboring tissue.

HEREDITARY. There is a frequent familial occurrence, and a high rate of consanguinity of parents which indicates a recessive type of heredity.

THE PORPHYRIAS

CLINICAL. The porphyrins, or blood pigments, are composed of a tetra-pyrrol nucleus. They contain no iron, and are important for the synthesis of hemoglobin and the respiratory enzymes. In pathologic concentrations they are severely toxic. Porphyrinuria may be secondary to an intoxication or to various diseases, or it may appear primarily as the result of a congenital or hereditary anomaly of porphyrin metabolism. Clinically and genetically, the primary forms of porphyria may be divided into (1) congenital (erythropoietic) porphyria, and (2) acute porphyria in adults (hepatic acute intermittent type, porphyria cutanea tarda, and the mixed forms).[14, 15] We shall be concerned only with congenital porphyria here.

This disease appears in early infancy or may be present at birth and manifest itself primarily by cutaneous symptoms due to the photosensitizing (photointoxicating) action of porphyrins. Exposure to light provokes the formation of necrosing cutaneous eruptions (hydroa vacciniforme) with widely distributed and deforming scars, specifically about the face, ears and hands. A brownish pigmentation is to be noted around the skin lesions, and hypertrichosis and alopecia also occur. A deep red urine and a brown color of the dental enamel are

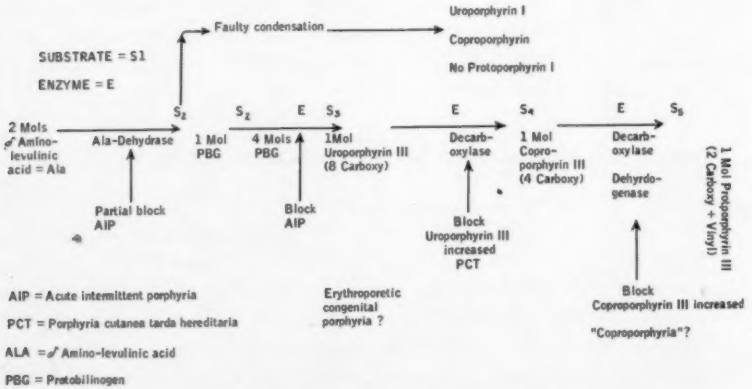


Fig. 2. Probable blocks in porphyria.

characteristic. Porphyrin deposits in the bones may produce a brown pigmentation which becomes visible on transillumination of the hands. The eye may also be photosensitive with consequent development of ectropion, corneal opacities, cataract and scleromalacia.

Chronic porphyrinuria is a form of the disease which may occur in late infancy or in the adult, which shows cutaneous lesions and photosensitivity; it may be latent.

HEREDITARY. Acute porphyria (including hepatic acute intermittent type and porphyria cutanea tarda, as well as the mixed, all occurring in adults and not discussed here) is transmitted as a dominant. Congenital porphyria is usually of a recessive pattern with a high frequency of consanguinity of affected families. It has been known to occur in monovular twins.

IDIOPATHIC FAMILIAL METHEMOGLOBINEMIA

CLINICAL. This rare congenital anomaly is characterized by the presence of an increased proportion of methemoglobin in the blood, due to a specific enzyme deficiency of the oxidation-reduction system in

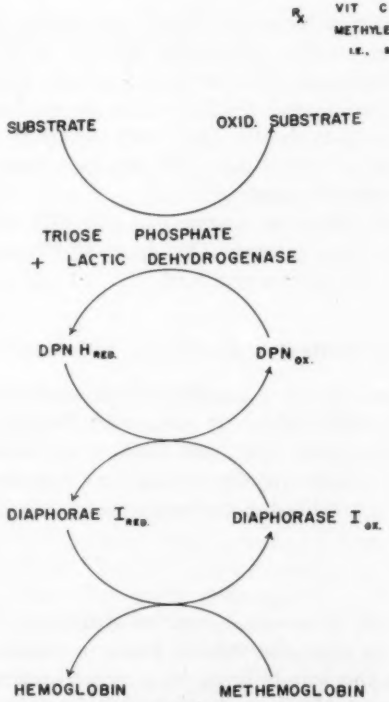


Fig. 3. Methemoglobinemia.

the erythrocyte (Fig. 3). Affected persons have a strikingly cyanotic appearance. Methylene blue or ascorbic acid may in some instances substitute for the lacking oxidation-reduction system.

HEREDITARY. Pedigrees suggest a recessive inheritance.

HEMOCHROMATOSIS

CLINICAL. This disease is characterized classically by (1) hepatosplenomegaly, (2) a slate-blue-gray color of the skin and mucosae, and (3) severe diabetes. It may occur in the juvenile form, characterized by endocrine disturbances and a rapidly progressive hepatomyocardial failure.

HEREDITARY. Consanguinity has been observed in the parents, suggesting a recessive inheritance.

DISEASES OF ECTODERMAL CELLS

ICHTHYOSIS

Ichthyosis Congenita

CLINICAL. This disease is present at birth, and occurs in both sexes in varying degrees of severity. *Harlequin fetus* is incompatible with life. Large horny plates cover the entire skin surface with deep fissuring between them; feeding and respiration are impossible. The infant is either born dead or dies shortly after birth. There is usually severe deformity at the site of the plates; and the face, ears, hands, feet, and so on, may be severely distorted.

Milder cases occur which are compatible with life, in which large or small blisters are often present. This form of the disease appears to be a variation of the more severe type.

Congenital Ichthyosiform Erythroderma

CLINICAL. This appears to be a variation of the congenital ichthyosis, with a typical universally red, shiny skin, with flexural fissuring and bulla formation. The hands, feet and flexures are affected, and the nails may be absent. Subsequently scaling and hyperkeratosis occur, and by the time of adult life the erythroderma usually disappears.

Ichthyosis Vulgaris

CLINICAL. This is the commonest type of ichthyosis, and occurs in all degrees of severity from the mildest form, in which follicular pinhead papules cover the hair follicles, to a generalized xerodermia. In the severe types, sweat glands and sebaceous glands are rudimentary

or absent. The extensor aspects of the limbs and trunk are commonly involved, and the flexures, axillae, face, palms and soles are usually spared, suggesting that this disease has a different origin than ichthyosis congenita.

Tylosis Palmaris et Plantaris

CLINICAL. This disease is common. It may be present at birth, or the onset may be delayed until the child is five or six years old. The disease process consists in a symmetrical thickening, sometimes very severe, of the skin of the palms, soles and flexor aspects of the digits. There is an associated hyperhidrosis of the affected areas. The margins of the affected areas are usually pink and sharply demarcated. Histologically, all layers of the epidermis are thickened, but most particularly the horny layer. The sweat glands are increased in number and have dilated ducts. When the hyperkeratotic mass is shed or removed, the base is tender or erythematous. The soles may be very tender, and gangrene has been reported as the result of constriction of digital vessels.

Hereditary Aspects of Ichthyosis

Ichthyosis congenita and congenital ichthyosiform erythrodermia appear to be due to recessive genes. Ichthyosis vulgaris, on the other hand, appears to be due to a dominant autosomal gene. There is some evidence in certain pedigrees that ichthyosis vulgaris may be inherited as a sex-linked recessive, clinically similar to that produced by the dominant gene. Tylosis appears to be transmitted by a single dominant autosomal gene of high penetrance. No race is immune. Associated abnormalities are rare.

CONGENITAL ANHIDROTIC ECTODERMAL DEFECT

CLINICAL. This disease is characterized by agenesis of the epidermis and its appendages. The hair is fine and sparse; the teeth are absent or deficient with peg-shaped incisors and misshapen molars; the sweat, sebaceous, mammary and even lacrimal glands are absent or rudimentary; the mucous glands of the nose are often absent; the nails may be dystrophic; milium bodies are seen on the face; and cataracts have been reported. The patients are usually of normal intelligence with poor physique. The tooth abnormalities and the dry, anhidrotic skin are the usual causes of symptoms. It is probable that a single gene is responsible for the multiplicity of effects observed, and that it causes its effects at a crucial period during embryonic development.

HEREDITARY. Most cases appear to be a sex-linked recessive type of

inheritance, since males are much more commonly affected or the female heterozygotes are not always completely normal.

BENIGN FAMILIAL PEMPHIGUS (HAILEY AND HAILEY'S DISEASE)

CLINICAL. This is a rare bullous disease in which the eruption occurs most commonly around the neck, in the axillae and in the groin. It is usually preceded by some irritation or burning sensation. Pressure, friction and heat appear to be the exciting factors. Histology shows intraepidermal cleft formation, leading to the appearance of vesicles and bullae. There is dyskeratosis and acantholysis. Rounded acantholytic cells, either singly or in clumps, line the cleft and may lie freely within it. The basal cell layer is intact. The acantholytic cells differ from those seen in true pemphigus by the fact that their nuclei are *not* degenerating, and have even been seen to undergo mitosis.

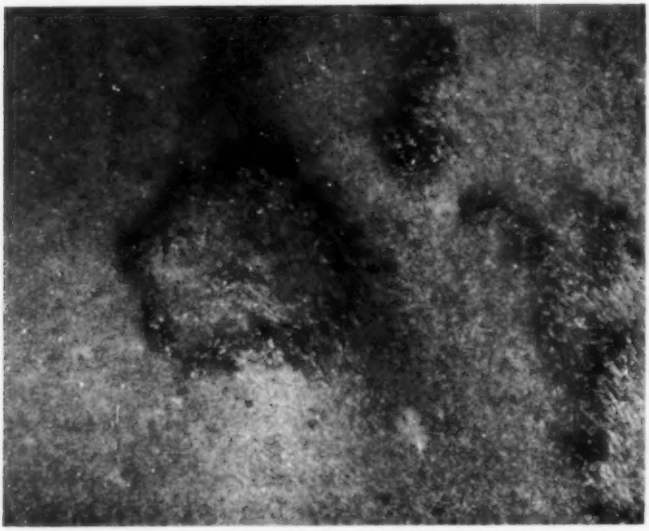


Fig. 4. Benign familial pemphigus (Hailey and Hailey's disease).

HEREDITARY. There is usually a family history suggesting that inheritance is due to a single dominant gene. The disease appears to be distinct from Darier's disease.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS)

CLINICAL. This disease is essentially a dyskeratosis, and usually begins in childhood. It is characterized by numerous discrete follicular

papules which, as they enlarge, become gray or brown and crusty. The head, neck, back, chest, abdomen and groin may be affected, and less commonly the backs of the hands and dorsal surfaces of the feet. The palms and soles are extensively involved with minute lesions which show up on palm-printing and finger-printing. As the disease progresses the papules tend to coalesce to form small nodules or tumors. Ulceration with secondary infection may occur, especially in the groin and axillae. Histologically, hyperkeratosis, follicular plugging, acanthosis and cleft formation occur in the prickle cell layer. Corps ronds occur in the neighborhood of the clefts or lacunae. These are dyskeratotic prickle cells and are diagnostic. Clinically, this disease must be differentiated from benign familial pemphigus.

HEREDITARY. This disease appears to be familial and due to a single dominant gene affecting both males and females equally.

XERODERMA PIGMENTOSUM AND MULTIPLE BASAL-CELL CARCINOMA

CLINICAL. Crocker called this disease, first described by Kaposi in 1870, atrophoderma pigmentosa. The skin reacts abnormally to light, particularly ultraviolet light. Freckles, pigmentation, telangiectasia, localized atrophy, warty growths, superficial ulcers and malignant changes appear, frequently in that order. The exposed parts are especially affected, in male as often as in female patients. The earliest signs are usually reddening and excessive freckling of exposed parts in the first summer of the infant's life. Conjunctival injection and photophobia may be observed earlier. In following years hyperkeratosis, melanin pigmentation, telangiectasia and atrophy occur. The early histologic change consists in epidermal hyperplasia and dermal atrophy, particularly of the papillary processes. Later a vascular dilatation and atrophy of the collagen and elastic tissue occur, associated with hyperkeratosis and occasionally metaplasia. Basal-cell carcinomas frequently develop; squamous-cell carcinomas more rarely; but melanocarcinoma, sarcoma and malignant endothelioma have also been reported. Malignant change may also occur on the conjunctiva.

Severe mutilation of affected parts results from scarring and atrophy. Death usually occurs before the age of 30. The disease occurs in Negroes despite their pigmentary advantage. The disease has been described in Jews more frequently than in Gentiles.

HEREDITARY. This disease is considered by some to be due to an incompletely sex-linked recessive gene occurring on the homologous portion of the sex chromosome. In heterozygotes the exposed areas of the skin are heavily freckled and unduly sensitive to sunlight, but the other changes usually do not occur.

PACHYONYCHIA CONGENITA

CLINICAL. This is a rare disease, which includes dystrophy of the nails, hyperkeratosis of the palms and soles, hyperhidrosis, follicular hyperkeratosis leading to warty growths around the large joints, white patches on the tongue, and corneal dyskeratosis. The heaped-up, claw-like nails are usually present at birth, constituting the most constant feature of the disease. The other characteristics described occur later. The essential histologic abnormality is dyskeratosis with hyperkeratosis and follicular plugging.

HEREDITARY. The heredity in this disorder is at present not clear. Cockayne, however, considered the defect to be due to two autosomal dominant genes, neither of which alone caused the abnormality.

POROKERATOSIS

CLINICAL. This abnormality, usually first seen in childhood, is progressive and chronic, affecting the palms, soles, forearm, legs, face and trunk. The essential lesion is a hyperkeratotic papule or collarette, which enlarges by peripheral extension; the central area of skin may become atrophic and depressed. The expanding border may be hard, raised and thickened, and have a sharp furrow or groove running along its peak. The hairs may be shed or replaced by horny plugging of the follicles. The hyperkeratosis and atrophy are more pronounced on the hands and feet and sites of friction, while the hyperkeratosis on the abdomen, thighs and face may be mild with minimal atrophy. Histologically, there is a hyperkeratosis of the involved areas, most prominent at the edge where there is a horny plug at the site of the groove. Parakeratosis is present. There is acanthosis and later atrophy of the prickle-cell layer, and lymphocytic infiltration of the epidermis followed by atrophy of the appendages and collagen degeneration.

HEREDITARY. This disease appears to be consistently due to a dominant autosomal gene.

PILI TORTI

CLINICAL. This disorder appears in children who have been bald for the first year or two of life. The hairs of the scalp are usually short and are found to be twisted through 180 degrees on their own axes at irregular intervals. They are readily broken. Occasionally the eyebrows and eyelashes are also affected. Twisting of the hair shaft is usually due to the irregular growth in the follicle.

HEREDITARY. This condition, most often seen in isolated cases as a

dominant, may likewise occur in families as an irregular dominant. The condition has also been reported in twins.

MONILETHRIX

CLINICAL. This disease usually first appears in childhood, when the beading and fragility of the hairs leads to breakage about 5 to 10 mm. from the scalp. There is a gradually progressing alopecia and associated keratosis pilaris. The beading of the hair shaft can be observed with a lens, and consists of alternating normal and atrophic segments of hair.

HEREDITARY. Monilethrix appears to be due to a single, irregularly dominant gene. It occurs almost invariably in dark-haired persons.

PITYRIASIS RUBRA PILARIS

CLINICAL. This is a chronic exfoliative disease of the skin, usually appearing in childhood. The essential lesion is a discrete acuminate papule situated over the opening of the pilosebaceous follicle. The papule is horny, blocking the opening and projecting with the hair in a small cone-shaped spine. The disease usually occurs first on the face as dry, adherent scales, and subsequently appears on other parts of the body. The typical papules give the skin a nutmeg-grater or gooseflesh appearance. As the disease progresses, scaling becomes more evident, and erythema is present. Severe palmar and plantar hyperkeratosis develops; the nails are often roughened and striated transversely. Histologically, there is hyperkeratosis, patchy parakeratosis (particularly around the openings of hair follicles) and acanthosis. The dermis may show mild chronic inflammatory changes. The health is usually unimpaired, although the disease may advance and become generalized.

HEREDITARY. This disease appears to be due to a dominant gene of high penetrance. No associated abnormalities have been described.

DISEASES OF THE MESODERMAL CELLS

EPIDERMOLYSIS BULLOSA

The simple and the dystrophic forms of this disease have been recognized, which correspond to the geneticist's dominant and recessive types. There is not complete correspondence between these classifications, for though the simple form is inherited as a dominant, the dystrophic form may be either dominant or recessive.

Simple Epidermolysis Bullosa

CLINICAL. This disease appears in the first year of life. The bullae are always traumatic in origin, and occur most frequently in hot weather. The bullae, occurring at sites of trauma on fingers, knuckles, toes, ankles, and elsewhere, are superficial, heal without scarring, and leave only temporary pigmentation. There are no epidermal cysts, and Nikolsky's sign is absent. The bullae are intraepidermal, small or medium-sized, and the contents are clear.

HEREDITARY. The heredity is irregularly dominant.

Dystrophic Epidermolysis Bullosa (Hyperplastic Type)

CLINICAL. This type develops at any time between birth and puberty. The bullae are usually traumatic, but may occur spontaneously, and they are most commonly confined to the head and limbs. The mucous membranes may be affected in about 20 per cent of cases. The bullae are intraepidermal and are at the epidermo-dermal junction. They may be small or medium-sized, tense, with clear contents, but occasionally may be hemorrhagic. Deeper subepidermal bullae occur, healing with scarring and keloid formation. Epidermal cysts may be present, and the Nikolsky sign may also be present. The lesions consist of lichenoid white papules, 1 to 2 mm. in diameter, occurring predominantly in the seborrheic areas. The dilated openings of the sebaceous ducts may be seen in the center of the papules, which are not related to the bullae. Acne vulgaris frequently occurs with this disease. Ichthyosis, palmar and plantar keratosis, hyperhidrosis, keratosis pilaris, mucosal keratoses, thickened and deformed nails, and hypertrichosis may accompany this disorder.

HEREDITARY. Inheritance is due to a single autosomal gene of high penetrance.

Dystrophic Epidermolysis Bullosa (Hypoplastic Type)

CLINICAL. Onset usually occurs at or soon after birth. Bullae arise spontaneously on any part of the skin, their appearance showing no seasonal variation. The mucous membranes are usually affected. The bullae generally occur at the dermo-epidermal junction and are accompanied by lesions of the vessels and neighboring elastic tissue. They are medium-sized to very large, and are often flaccid and hemorrhagic. Epidermal cysts are common, and scarring is the rule. Nikolsky's sign is usually present. Associated hyperplastic abnormalities frequently occur, such as absent or rudimentary nails; thin, xerodermic, presenile skin; atrophic, sometimes acrosclerotic finger tips; hypoplasia and

malformation of the teeth. In addition, there may be corneal involvement and hypotrichosis. Abnormalities of the blood and endocrine system may be apparent, and there may be associated psychiatric disorders. Porphyria may be concomitantly present. Death may occur in utero, during the first days of life, or later.

HEREDITARY. This disease appears to be due to a single recessive gene.

What the genetic relationship of these three disorders is, is not clear. There is no known relation between the simple dominant and recessive genes.

RECURRENT BULLOUS ERUPTION OF THE FEET

CLINICAL. This disease is normally seen in infancy and occurs throughout life in the hot summer weather. Hyperhidrosis is a common accompaniment. Disability is severe, and walking may be impossible. Healing occurs without scar formation. Blisters may vary in size from 1 to 5 cm. in diameter, but occur only on the soles of the feet. The fact that blisters do not occur elsewhere and that there are no other signs of epidermolysis bullosa suggests that this disease is clinically discrete.

HEREDITARY. This disease seems to be due to a single dominant gene, and occurs slightly more frequently in males.

HEREDITARY HEMORRHAGIC TELANGIECTASIA (RENDU-OSLER-WEBER DISEASE)

CLINICAL. This disease usually occurs in childhood, but may not become manifest until the patient is 30 years old or over. There are repeated episodes of bleeding and telangiectasia and a family history of one or both of these. The multiple telangiectasias appear most commonly on the face and on the mucous membranes of the nose and mouth, on the conjunctiva, and beneath the nails. They may be small or large, and show a central nodule of vascular tissue. Epistaxis may be severe, and is usually the first and commonest symptom, generally preceding the onset of cutaneous telangiectasia. Postmortem and clinical examinations have demonstrated that the throat, bronchi, lungs, kidneys, bladder and gastrointestinal tract may be involved, leading to unexplained bleeding. Anemia is common, and death may occur from hemorrhage.

HEREDITARY. This disease appears to be caused by a single regularly dominant gene. Males and females are equally affected. It appears to occur more frequently in Jews than in Gentiles.

URTICARIA PIGMENTOSA

CLINICAL. There are two forms of this disease, the adult and childhood varieties. Clinically, the disease is characterized by red-brown or brown pigmented nodules or macules which form wheals on friction or when the patient becomes hot. Lesions are usually distributed symmetrically over the trunk, back and limbs. In the childhood form of the disease vesicles and bullae are often seen. These tend to disappear as the child grows older, with the appearance of typical macules and nodules in their stead. The lesions tend to fade with age, and occur more commonly in fair children. (See also page 860 ff.)

HEREDITARY. The hereditary aspects of this disease have not been completely worked out, but a recessive inheritance appears most likely at the present time, although consanguinity has not been demonstrated to date.

EPILOIA

CLINICAL. In this rare disease epilepsy and the appearance of mental defects may be associated with tumors of the brain, skin and viscera, especially the heart and kidneys. The syndrome of adenoma sebaceum, epilepsy, and mental deficiency has long been recognized under the term "epiloia." The disease usually manifests itself in early childhood when the skin lesions appear. These take the form of small papules on the "butterfly" areas of the face. With increasing age the papules enlarge and become more numerous, and form nodules and small tumors 1 to 10 mm. in diameter with a yellow to red-brown cast. The upper lip is typically spared. Histologically, there is increased growth of sebaceous gland tissue and epidermal thinning. Telangiectasia may be prominent, and the face may be permanently scarlet. Pigmented and warty nevi of the face may be present. Periungual and subungual fibromas are typical. Fibromas may also occur in the mouth and nose. "Shagreen patches," consisting of raised, thickened connective tissue plaques, are found in the lumbosacral region, and a *café-au-lait* pigmentation similar to that found in von Recklinghausen's disease may be present.

In addition to the cutaneous manifestations, tumors occur in the brain, heart and kidney. Kidney tumors may be sarcomas, fibromas or hypernephromas. Tumors of the heart are usually multiple rhabdomyomas. Tumors have also been reported in the liver, spleen, lungs, duodenum, thyroid and thymus; and retinal tumors have been observed. Tumors of the brain measuring 5 to 50 mm. in diameter consist mainly of neuroglia and astrocytes. They frequently undergo

degeneration. Depending upon their size and location, they cause epilepsy, exophthalmos and mental deficiency.

HEREDITARY. An irregular dominant gene with variable degrees of expression has been invoked. Penrose[12] considers that a modifying autosomal dominant gene influences the pathogenic gene, giving rise to variations in phenotypical expression and, therefore, being responsible for the variations in clinical pattern. Thus epiloia is probably due to a single dominant gene which may be affected by a modifying gene. The cutaneous manifestation, adenoma sebaceum, is regarded as only part of the total disease picture.

MULTIPLE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

CLINICAL. This disease is relatively common and occurs in both sexes and in all races. It is characterized by the presence of multiple sessile or pedunculated tumors irregularly disseminated over the skin. Frequently the tumors occur along the course of deep and subcutaneous nerves, and there is a brown pigmentation of the skin and mucous membranes. The tumors may be soft or firm, and vary in size from several millimeters to 10 cm. or more in diameter. The tumors are derived from nerve sheath and are frequently found on the acoustic nerve. When situated on or near deep organs, especially those in confined spaces, such as the pituitary or brain, they produce extensive changes from pressure and destruction. They are not infrequently associated with the adrenal gland, thyroid gland and parathyroid gland.

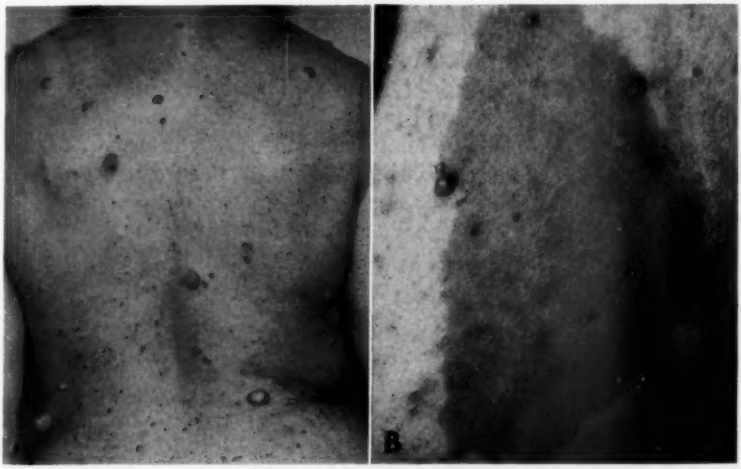


Fig. 5. Multiple neurofibromatosis (von Recklinghausen's disease). *A*, Showing characteristic tumors. *B*, Showing *café-au-lait* spot and tumors.

The changes occurring due to pressure are secondary, and deafness, mental disorders, skeletal defects and glandular dysfunctions occur as a consequence. The tumors may rarely undergo sarcomatous metaplasia; this occurs in less than 5 per cent of cases. Pigmentation may vary in intensity and may be patchy. The disease is essentially benign, but disfiguring.

HEREDITARY. Affected members of the same family tend to show more or less similar clinical pictures, but different families vary considerably in the degree of tumor formation and in pigmentation. The situation of the deeper tumors also appears to be under genetic control. In most of the described cases the disease appears to be inherited as a strongly dominant character with a high degree of penetrance and a variable degree of expression. It has been suggested that a modifying gene may influence the observed picture.

PSORIASIS

CLINICAL. Psoriasis is a chronic disease and is observed in about 5 per cent of all outpatients seen in dermatology clinics. The essential lesions are reddish-brown, scaly papules which form aggregates of various shapes and sizes and are characteristically covered by a micaceous scale. The most commonly affected areas are the scalp and extensor surfaces, particularly the knees and elbows. The nails may be affected with brittleness, pitting and thickening. Pustular psoriasis occurs on the palms and soles. Rheumatoid disease and other forms of arthritis are frequently seen; arthropathic psoriasis is reserved for those cases in which the terminal interphalangeal joint is typically affected.

HEREDITARY. The etiology of psoriasis is obscure, but there is no question that this disease "runs in families." Lerner[10] demonstrated an incidence of 42 per cent in immediate relatives of probands. Others have found a comparable percentage of familial incidence. The disease appears to be due to a single autosomal gene acting as an irregular dominant, though recessive pedigrees have been reported.

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PHARMACOLOGY OF TOPICAL THERAPY

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The advent of antibiotic and anti-inflammatory steroid preparations which can be applied topically has marked the greatest advances in topical therapy in the last hundred years. Otherwise, topical therapy has scarcely participated in the tremendous progress of modern medicine. Rather, it has been a time-honored, empirical branch of medicine, more a product of medical art than of science, but so useful as to be retained in modern practice with relatively minor modifications since the second half of the last century.*

PHARMACOLOGIC PRINCIPLES OF TOPICAL MEDICATION

In many respects these principles differ from those of internal medication. In topical application one ordinarily thinks in terms of concentration of the medicament because the effect of the drug which has been incorporated into a vehicle is intensified roughly in proportion to concentration and not to the absolute amount applied. Total quantity, however, must also be considered if drugs which are absorbed through the skin are applied over large areas of the body surface and thus can possibly cause systemic effects. This consideration is particularly important in pediatric practice. In past times, for example, sulfur ointments applied over the entire body surface of infants for the treatment of scabies led in some instances to severe or even fatal systemic sulfide

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* Cf. S. Rothman and A. L. Shapiro: The Pharmacodynamics of Vehicles and Drugs in Dermatologic Therapy. *M. Clin. North America*, 33:263, 1949.

poisoning. Also, the use of highly concentrated tar preparations in extensive infantile eczema has led to nephritis as a consequence of systemic absorption.

Application over large surfaces of the currently used topical steroid preparations has so far not resulted in the development of undesirable side effects with the remarkable exception of fluorohydrocortisone, which has caused severe salt and water retention in some cases.[1] Still, one should use topical steroids with some caution, particularly in infants with widespread infantile eczema. Although percutaneous absorption of steroids through intact skin is almost negligible, absorption through "broken skin," meaning lesions where the subcorneal barrier membrane to absorption has been damaged, may be considerable.[2] In eczematous lesions and in scratch marks there is severe impairment of this subcorneal barrier. Thus it is our belief that the Food and Drug Administration was wise in its decision in 1956 not to permit across-the-counter sale of these preparations.[4] An unhappy and impatient mother whose baby scratches and cries all night may apply with absurd frequency such extreme amounts that the quantity of steroids absorbed may indeed lead to serious degrees of hypercorticoidism and adrenal suppression. Thus, in spite of lack of documented damage from the topical use of corticosteroids, it has been advisable to dispense these materials only on prescription by physicians who keep track of the amounts dispensed.

Maximum or minimum concentrations of topically applied drugs have not been clearly established in contrast with the way dosages are established for internal medication. Even average concentrations have not been specified. On the contrary, most topically applied remedies are used in widely different ranges of concentration. Moreover, the pharmacologic action of a topical medicament may vary according to concentration. For instance, silver nitrate is used in dermatologic wet dressings for anti-inflammatory effects in acute oozing dermatitides in concentrations of 1:20,000 to 1:10,000; as an antiseptic and for stimulating granulation in torpid wounds in 1 to 2 per cent concentration; and in still higher concentrations or in "stick" form as a caustic agent for destruction of redundant granulation tissue.

A most significant point which emphasizes the special position of topical pharmacology is the fact that the kind of vehicle used is of paramount importance, because the pharmacologic actions of incorporated drugs may vary according to the nature of the vehicle. Salicylic acid, for example, has different effects in the same concentration, depending on whether it is incorporated into a powder, lotion, paste, ointment or plaster. Its keratolytic effect increases tremendously with the vehicles in the order listed.

By definition, "vehicles" or carriers of drugs are chemically and

pharmacologically inert materials. But in topical applications they may have therapeutic actions based on their physical properties. This physical action is often significant enough so that in dermatotherapy plain vehicles are often used without incorporated medicaments.

PHARMACOLOGIC EFFECTS OF TOPICAL APPLICATIONS

The major pharmacologic effects which can be achieved by topical applications can be listed as follows:

1. Anti-inflammatory effects in acute inflammation—cooling, vasoconstrictor, and anti-exudative or "astringent" effects (antiphlogistic effects).
2. Symptomatic relief of itch and pain (antipruritic and analgesic effects).
3. Cleansing—removal of exudate, crusts, scales, dirt and previous applications.
4. Protection from mechanical, thermal, actinic, and chemical irritation.
5. Alleviation of "dryness" or chappiness resulting from decreased water-holding capacity of the horny layer (emollient effect).
6. The killing or hindering of growth of microorganisms in or on the skin (antibacterial, antifungal, antiviral and antiparasitic effects).
7. Reduction of manifestations of subacute and chronic inflammatory processes ("reducing" effect).
8. Dissolution of excess horny material (keratolytic effect).
9. Chemical destruction of pathologic tissues (caustic effect).
10. Regulation of excessive lipid secretion (antiseborrheic effect).
11. Regulation of excessive sweat secretion (antihidrotic effect).

PHARMACOLOGY OF VEHICLES

Solutions

Mildly astringent aqueous solutions are applied as dermatologic or open wet dressings in acute and subacute inflammatory processes of the skin when there is oozing and crusting due to epidermal damage, as may be the case in contact dermatitis, including infantile eczema.

These dressings are applied as follows: a piece of white cotton cloth (old handkerchiefs or bed linen, for example) is soaked in the solution at room temperature, wrung out and applied to the involved area. The fluid-saturated (but not dripping) cloth is left uncovered to allow for free evaporation. Every 5 to 10 minutes, before the dressing starts to become warm and dry, it is removed, again soaked in the solution, wrung out and reapplied to the inflamed area. There is no legitimate short cut to this procedure. It is a wrong practice to reapply the solu-

tion from a syringe without removing the cloth, because water evaporates, while the solute does not, and thus the concentration of the solute gradually increases and may cause irritation. Furthermore, the gentle cleansing action of the procedure would largely be lost. Such wet dressings are applied over periods of one to one and a half hours, two to four times daily, depending upon the severity of the inflammation and particularly on the degree of oozing, crusting, pain or itching. Longer periods are not advisable because of the danger of maceration from prolonged contact with water.

In order to avoid undue chilling of the patient only restricted areas should be treated at one time.

The application of wet dressings in this manner is time consuming and in small children requires full-time assistance. Nevertheless their favorable influence, both objectively and subjectively, on hyperacute inflammatory processes with epidermal breakdown is unparalleled, and the time put in pays off. Usually there is no need to continue them for more than two or at most three days. More prolonged application of frequent wet dressings is not advisable because the resulting maceration (hydration of the horny layer) may promote bacterial or fungal (especially monilial) infections.

Recommended solutes commonly used in preparing solutions for wet dressings are potassium permanganate, silver nitrate and aluminum subacetate. In cases of extreme irritability saline solutions can be used. Potassium permanganate is used in 1:16,000 to 1:8,000 dilution (a crushed 1-grain tablet completely dissolved in a pint of water yields a 1:9000 solution). It stains skin and clothing and should not be used on the face. Silver nitrate, which also may cause unpleasant staining, is used in 1:20,000 to 1:10,000 dilution. Aluminum subacetate solutions, dispensed as Burow's solution, should be diluted at least 1:100. A commercial preparation (Domeboro tablets) has more constant composition and yields the right pH in aqueous solution. One tablet is usually dissolved in 1 quart of water.

The rationale in the use of these active agents is that they are astringents; they precipitate proteins and thus decrease oozing. They also have a little of antibacterial and antifungal actions. The main effectiveness of wet dressings, however, is based on the free evaporation of water which causes cooling. Cooling in turn effects vasoconstriction and relieves itching and burning.

Powders

Dusting powders are useful when moisture has to be absorbed on more or less intact skin surfaces. In the past they were used to prevent maceration in intertriginous areas in infants, and it is regrettable that

in modern times attempts are being made to displace them with other modalities. Bland dusting powders are extremely useful in the prevention of diaper rashes, in all forms of miliaria or prickly heat (an extremely common and often misdiagnosed condition in the infant), and in the care of normal skin in intertriginous areas.

A mixture of equal parts of zinc oxide and talc is a good and inexpensive powder base. Sometimes it is advisable to add small amounts of greasy material. An old and excellent prescription form is spermaceti, 0.5 per cent in equal parts of zinc oxide and talc. Vegetable powders such as corn starch are smooth and effective moisture absorbers, but they tend to support microbial growth and to be unstable and so are not recommended.

Lotions

Lotions are unstable suspensions of dusting powders in aqueous liquids with some added hygroscopic material, usually glycerin. If, immediately after vigorous shaking, such a suspension is painted on the skin with a soft paint brush, it exerts a cooling effect similar to that of wet dressings. It has the advantage that in order to maintain its cooling effect it has to be repainted only three to four times a day. On reapplication the old layer need not be removed. Furthermore, after most of the water has evaporated, the powder particles form a protective layer which adheres because of the viscous nature and binding power of the hygroscopic agent. It has the disadvantage, however, that it cannot be applied to oozing or crusting lesions. It will not adhere to an oozing area and may make crusts more occlusive, thus promoting bacterial growth and absorption of cellular and bacterial decomposition products. Lotions should not be applied to hairy regions because they cake the hair and are difficult to remove. In intertriginous areas shake lotions are used only exceptionally because there is no free evaporation of water. Wet dressings and lotions have the same general purpose and action, namely, cooling by water evaporation.

The classic example of a lotion is calamine lotion USP. Its powder content is rather low, and many practitioners prefer lotions with a higher powder content because of the more protective dense surface film which is left on the skin a few minutes after application. A useful formula is as follows:

Zinc oxide Talc, aa.	54.0
Glycerin	24.0
Aqua dest. q.s. ad	240.0

Sig.: Shake well. Apply with soft brush p.r.n.

This formula, if used for prolonged periods of time on children's

skin, may cause chappiness. Therefore addition of 10 per cent olive oil is recommended:

Zinc oxide	
Talc, aa.	54.0
Glycerin	24.0
Olive oil, aa.	24.0
Aqua dest. q.s. ad	240.0

Lotions are useful carriers of active drugs such as sulfur or resorcin in the treatment of acne.

Liniments

Liniments are oil-in-water emulsions with or without added powder. They serve similar purposes as lotions, but have greater built-in protection against overdrying by virtue of their high oil content. They do not dry promptly and, therefore, are preferably applied under bandages. The formula of calamine liniment is as follows:

Calamine	
Zinc oxide, aa.	80.0
Olive oil	500 ml.
Calcium hydroxide solution q.s. ad	1000 ml.

In prescriptions of calamine liniment it should be specified that the plain base is meant, because for antipruritic purposes most calamine liniments contain phenol, which in pediatric practice is a potentially dangerous constituent.

Pastes

These are mixtures of powders and ointments. In older formulas, paste of zinc oxide contained 50 per cent powder and 50 per cent ointment. In modern formularies so-called softer pastes with a powder content not higher than 30 per cent are preferred. Thus "zinc oxide ointment" USP containing 20 per cent zinc oxide in petrolatum and wool fat is a paste, although called an ointment.

The powder content acts by adsorbing moisture, and pastes, therefore, have a drying effect. Pastes are used in acute, subacute or chronic inflammatory conditions if a rather mild effect of the incorporated medicament is desired. For instance, salicylic acid, sulfur and tars have a milder effect, i.e. less irritating though therapeutically less effective action, if incorporated into a paste rather than into an ointment without powder content.

The difference in action is apparently due to the fact that an ointment is more occlusive than a paste in which fine powder particles interrupt the continuous phase of the ointment (see p. 704).

Pastes are thickly spread with a tongue blade or the handle of a clean spoon onto the skin. A dressing must be applied with at least one layer of soft linen before gauze layers or gauze roll bandages are put on. Dressings are changed twice or three times daily. To change a dressing, the older hardened layer of paste is first softened by patting with oil and then removed by gentle wiping with an oil-soaked piece of soft cotton material, but no attempt should be made to remove all the paste.

Ointments

These are substances of a greasy consistency which can be spread on the skin in a continuous layer, and are used for therapeutic purposes with or without incorporated drugs.

Ointments are made of (1) animal subcutaneous fats such as lard (glycerides of palmitic, stearic and oleic acids); (2) minerals such as petrolatum (hydrocarbons); (3) animal skin fats such as wool fat (a rather complex mixture of neutral fats, waxes, fatty acids, and sterols). Lard is a useful lubricant for dry irritated skin and for cleansing. Modern additives for the prevention of rancidity such as butylated hydroxy-anisole and propyl-gallate contained in packaged lard of the major meatpacking companies have proved to be nonirritating. Some patients or parents, however, object to the smell of lard.

Liquid oils such as vegetable oils (e.g. olive oil, linseed oil) and mineral oils (light mineral oil) are not true ointment bases, but are frequently used as cleansing agents in place of soap and water, which are often poorly tolerated in most acute and in some subacute inflammatory dermatoses.

Petrolatum (Vaseline) is the most widely used ointment base because it is chemically inert and stable. Both the yellow and the bleached white petrolatum are listed in the United States Pharmacopeia. In some patients with irritable skin, yellow petrolatum seems to be better tolerated than the white.

Wool fat or anhydrous lanolin is the purified fat from sheep's wool. Lanolin is wool fat with 25 to 30 per cent water. Miscibility with water makes wool fat different from the previously mentioned ointment bases. Under pressure twice its weight of water can be incorporated into wool fat because its sterols and waxes act as emulsifiers. The resulting emulsion is of the water-in-oil type, the grease being the continuous phase in which droplets of water are dispersed. On the skin surface water slowly evaporates from such a system, thereby exerting a cooling effect. For this reason such systems are called "cold creams" and may be used for cooling, although their cooling effect is less pronounced than that of wet dressings and lotions.

Lanolin has a variable composition. An artificial lanolin-type material of constant composition has been prepared by cholesterolizing yellow petrolatum. It is marketed under the names of "Aquaphor" or "Eucerine."

The official cold cream or water-in-oil emulsion historically listed in the United States Pharmacopeia contains almond oil as neutral fat, white wax and spermaceti as emulsifiers, and water. There are a great number of similar, commercially available cold creams, i.e. water-in-oil emulsions, which are equal in quality.

In contrast to water-in-oil emulsions, the emulsions containing dispersed oil droplets in a continuous aqueous phase are less useful vehicles in the topical therapy of skin diseases. These are the "water-washable" and "vanishing cream" bases which have excellent applicability for cosmetic purposes, but are generally not well tolerated by inflamed or sensitive skin.

Among modern kinds of greasy bases are the carbowaxes. These are polymerized polyethylene glycols of molecular weights between 1000 and 4000. They are soluble in water and can be washed off easily. They have not attained great popularity in dermatotherapy. Similarly, the nonionic surface-active agents, Tweens and Spans, although thought to promote penetration of incorporated drugs, only rarely figure in dermatologic prescriptions.

In general, ointment bases occlude the skin surface and thus hinder water loss. Retention of water causes swelling of the horny layer, a condition which, under occlusive conditions, seems to lead to greater penetration of drugs. Therefore, in the same concentration drugs incorporated into ointments will have more intense effects than if incorporated into pastes, because the powder particles in the latter interrupt the continuity of the ointment layer. Lotions have even less occluding effect than pastes, and drugs incorporated into lotions have relatively the least (therapeutic and irritative) effects.

The most occlusive ointment bases are petrolatum and lard. Such bases should not be used in acute inflammatory processes, because water retention is associated with heat stasis, which in turn may aggravate acute inflammatory vasodilatation. Occlusiveness decreases with increasing water-miscibility. Minor occlusive effects of cold creams are counteracted by the cooling effect of water evaporation.

Vegetable oils such as olive oil are used mainly as cleansing agents in place of soap and water, which are poorly tolerated as cleansers in most acute and some subacute inflammatory dermatoses. Light mineral oil for the same purpose is considerably cheaper, but may not always be as well tolerated as olive oil. Vegetable and mineral oils are also used as vehicles in the treatment of diseases of the scalp.

Plasters

Adhesive plasters, made by depositing dissolved rubber and resins onto cloth backing, are used when complete occlusion is desired to get maximal therapeutic action from an incorporated drug, such as the keratolytic effect of salicylic acid in the treatment of calluses and hyperkeratotic warts. Plasters can be cut to fit the shape of the lesion.

Collodion

Collodion, chiefly cellulose tetranitrate in alcohol-ether solution ("flexible collodion"), when painted on the skin forms a thin, well adherent occlusive film. The admixture of lactic acid and salicylic acid into collodion yields excellent preparations for the treatment of common and, in some instances, of juvenile flat warts. In children the initial concentration of the acids is 3 per cent, but gradually it can be raised to 10 per cent each (salicylic acid, lactic acid, aa. 0.6 to 2.0; collodion q.s. ad. 20.0). The warts are painted with the collodion solution on three or four subsequent nights without removal of the old film, until the lesion becomes slightly sore, indicating a mild inflammatory reaction. When this reaction occurs, the film is removed and a rest period of two days is given. Afterwards one starts daily treatments again with two-day rest periods after each inflammatory reaction. Warts will usually disappear completely after four to six weeks of such treatment. The principle of this method is the use of relatively mild caustic agents to destroy a benign lesion layer by layer without permitting an excessive reaction and eventual sloughing.

Soaps

The use of soaps as vehicles for chemically active drugs is of limited value, since in ordinary cleansing the period of contact with the skin is too short to have an appreciable effect. Thus germicidal soaps such as those containing hexachlorophene are of little value in treating bacterial infections.

Some newer shampoos containing selenium or cadmium polysulfides to combat dandruff are not recommended for pediatric practice.

The choice of the right kind of soap in cases of diseased or irritable skin, if soaps are at all permissible, is of some significance. Chemically, a high degree of purity is essential, and in the authors' experience old-fashioned pure soaps, meaning sodium salts of fatty acids (e.g. Ivory Soap) are preferable in spite of their alkalinity in aqueous solution to modern soaps with admixture of synthetic detergents. Excessive use of soap and water, one of the rather common excesses of Western civiliza-

tion, carries the danger of making the skin chappy with all the consequences of asteatosis, particularly in winter. There seems to be less of a tendency to develop asteatosis if one uses superfatted soaps such as Basis Soap, which contains 2 per cent Aquaphor.

In acne and oleic seborrhea washing with alkaline soaps is a helpful therapeutic procedure. Soft soap USP (green soap, medicinal soft soap, sapo mollis) is a potassium soap and is a more effective cleanser, and because it even causes mild peeling, it is the soap of choice in these conditions and also in psoriasis. Tincture of green soap, the alcoholic solution of soft soap, is an excellent shampoo for adolescents with oleic seborrhea of the scalp.

Baths

As is the case with medicated soaps, in medicated baths contact with the medication is of rather short duration, particularly if the bath water is rinsed off with clear water as is ordinarily and properly done. Also the dilution of the drug is usually far too great for effective action.

It has been an old tradition to add starches to the bath water (so-called colloidal bath) in the belief that such addition increases the soothing effect of the bath. In the authors' experience addition of starch or oatmeal increases rather than decreases the tendency to chapping.

A good method for minimizing the possible harmful effects of a cleansing bath in subacute inflammatory processes is to dissolve a mild soap in the bath water in advance until the water becomes opalescent and then soak the child for a few minutes in the soap solution, the soaking being followed by thorough rinsing with clear water. This procedure has the great advantage that rubbing is avoided and the concentration of the soap in contact with the skin is low.

In general, for several reasons, in itching skin conditions baths with soap and water carry the danger of eliciting new itch attacks. If giving a bath is unavoidable, instructions to avoid rubbing should be given. Drying should be done by gentle patting with soft towels.

Dressings

Pastes and sometimes also ointments are applied under dressings which usually are changed twice daily (see Pastes). The paste or ointment layer should always be covered first with soft linen. On top of the closely woven linen, gauze and gauze dressings may be used. The introduction of "tubular gauze" dressings has greatly simplified the applica-

tion of dermatologic dressings. For instructions about how to apply dressings on different parts of the body the reader is referred to the excellent text of Sulzberger, Wolf and Witten.[5]

ANTI-INFLAMMATORY, ANTIPRURITIC AND PAIN-RELIEVING AGENTS

The advent of corticosteroid preparations for topical use was an important step in the progress of anti-inflammatory local therapy of skin diseases. Hydrocortisone and its derivatives in lotions, sprays, ointments and cold creams have become important tools in symptomatic treatment of acute and subacute eczematous eruptions such as contact dermatitis, atopic dermatitis, seborrheic dermatitis and intertrigo dermatitis. Steroids often act more promptly and more intensely than wet dressings, bland shake lotions or cold creams. This superior effect, however, cannot be relied upon entirely. In morphologically analogous situations which seem indistinguishable, they work in some instances and fail in others. We are unable to predict their effectiveness. It seems that their penetration is highly dependent on the status of the subcorneal barrier and the thickness of the epidermis. It is conspicuous how much more effective they are on eyelids and around the anus, where the epidermis is thin, than on other parts. On normal skin, in general, absorption amounts to only 1 or 2 per cent of the material applied.

Steroids are not applicable on oozing surfaces because they are quickly diluted, decomposed or washed off. They are also usually ineffective in those subacute and chronic processes where there is a reactive thickening of the epidermis. Thus local treatment with steroids has not become a panacea in the treatment of all infantile eczema and other eczematous conditions as was hoped for originally. In infants frequent application on large surfaces as mentioned earlier may not be without risks.

The danger of promoting bacterial infection by the local application of steroids can be well taken care of by the admixture of one of the topical antibiotic preparations. As a matter of fact, practically all topical steroid preparations can be purchased with such admixtures. With such preparations a possible danger is the promotion of *Candida albicans* infection. If such a danger exists, particularly in the presence of much moisture in intertriginous areas, admixture of Mycostatin (see below) is indicated.

Newer derivatives of hydrocortisone have greater anti-inflammatory effect than the parent natural hormone and, therefore, can be applied in lower concentrations. Hydrocortisone creams and ointments contain 1 per cent and 2.5 per cent; prednisolone 0.5 per cent; and triamcinolone

acetonide 0.1 per cent of the active ingredients. Corresponding lotions are available in plastic vials with or without antibiotics.

Old-fashioned but sometimes highly effective local antipruritic agents are menthol and phenol. Menthol acts directly on cold receptors, giving rise to a sensation of coolness and vasoconstriction, whereas phenol acts on nerve endings as a local anesthetic. Both substances are likely to irritate in higher concentrations. In lotions, pastes and ointments the concentration of menthol should not exceed 0.25 per cent, and that of phenol should not exceed 0.5 per cent. In infants it is better to avoid the use of menthol and phenol altogether, particularly on extensive areas, because of possible systemic toxic effects. In school children the use, together with dressings, of a soft paste containing 0.12 per cent menthol, 0.25 per cent phenol, and 20 per cent zinc oxide in equal parts of petrolatum and cold cream is a time-honored and excellent antipruritic measure, often far superior in effect to topically applied steroids.

The admixture of local anesthetics of the procaine and benzocaine groups to topical preparations to counteract itching should be absolutely avoided because of the allergy-inducing potency of all these preparations. Anyhow, most of these compounds do not substantially penetrate the unbroken skin, and so nerve endings remain unaffected. When the skin is broken, primary irritation or sensitization tends to occur more readily.

Some antihistaminics also have analgesic action and for a while had been used as local antipruritic agents. Like the "-caine" compounds, these antihistaminics proved to be notorious sensitizers, and their local use should be strictly avoided.

It is needless to emphasize to physicians that the mere local application of symptomatically effective antipruritic agents seldom suffices for obtaining satisfactory results. The cause of itching and the nature of the underlying ailment must be clarified whenever possible through the use of all available diagnostic methods. Correct diagnosis helps more than the best and most powerful steroid ointment. In scabies the most satisfactory antipruritic effect is obtained by the use of antiscabetics; in insect bites by extermination of the insect; in vulvar itching due to diabetes or moniliasis by antidiabetic or antimonilial therapy; in clearly allergic conditions such as contact dermatitis and acute urticaria by the elimination of causative allergens; in pruritus ani caused by intestinal worms by anthelmintics; and so on.

In pruritic subacute and chronic inflammation of poorly established origin and pathomechanism such as atopic dermatitis, tar preparations play the most prominent role as symptomatic antipruritics. Again, more can be achieved here with old-fashioned topical therapy than with steroids.

ANTIBACTERIAL, ANTIFUNGAL AND PARASITICIDAL AGENTS

It has become a generally accepted principle in topical therapy not to use antibiotics which may be useful or even lifesaving when systemically administered. The reason is twofold. Firstly, external applications are more likely to elicit allergic sensitizations which often hinder future, possibly vitally important internal administration. Secondly, the bacterial flora on the skin may develop resistance to important antibiotics and thus may contribute to the formidable problem of the emergence of antibiotic-resistant microbial strains. Anyhow, some of the most important internally useful antibiotic substances—sulfonamides, penicillin (with all its variants), streptomycin and the furan derivatives—are viscious sensitizers if applied to the skin.

Antibiotics which are not or are hardly ever used in systemic therapy because they are either too toxic or are not sufficiently effective and which are still very useful in topical application include bacitracin, tyrothricin (gramicidine and tyrocidine), neomycin and polymyxin B, the latter two being effective against gram-negative, as well as gram-positive, bacteria. A great number of good commercial preparations (lotions, ointments and creams) are available containing one or a combination of these compounds which can be used with great success in any bacterial infection of the skin such as the different forms of impetigo, staphylococcal folliculitides, sweat gland infections and secondary impetiginous infections in eczemas. With the exception of a few sporadic cases of sensitization reported after the use of neomycin ointments, these antibiotics are surprisingly free of irritating and sensitizing effects. Tetracyclines and erythromycin can also be applied locally without danger of sensitization.

With the advent of modern topical antibiotics the rapid extinction of impetigo epidemics in places where children congregate (e.g. boarding schools, summer camps) has become an easy task. Topical antibiotics have also proved to be extremely effective in combating malodorous perspiration, a condition which may represent a clinical problem in adolescents. Antibiotics act because the malodor is a consequence of bacterial decomposition of cutaneous substances or secretions.

Among the older bacteriostatic and bactericidal preparations, ammoniated mercury still has its place, particularly in wounds infected with such antibiotic-resistant organisms as pyocyaneus or proteus. The antiseptic action of ammoniated mercury is slow but steady. Mercuric ions, responsible for the action, are split off slowly and gradually in the acid medium of the skin surface. There is hardly any systemic absorption, and if they are applied to circumscribed areas in children, systemic mercury poisoning does not occur. Ammoniated mercury is used in 1 to 3 to 5 per cent concentrations in lotions, pastes, ointments

and creams. The mechanism of the great beneficial effectiveness of ammoniated mercury ointments in psoriasis is not understood.

Another, ancient but still useful antibacterial remedy is Balsam of Peru, mainly used in up to 10 per cent concentration on torpid, infected ulcers.

In ringworm infections caused by filamentous fungi or hyphomycetes the newly introduced antibiotic, griseofulvin, has greatly diminished the importance of topical applications, particularly in pediatric practice. In most ringworm diseases of the scalp in children, in which topical remedies always have been of questionable value, griseofulvin brings about complete cure with amazing rapidity and so far without causing undesired side effects (see also p. 766 ff).

In superficial fungus diseases with no invasion of the hair such as tinea circinata, tinea cruris and tinea pedis in adolescents local applications are still the method of choice. One may use highly diluted iodine solutions (e.g. 2 per cent iodine in benzole), sulfur ointments with or without salicylic acid, fatty acid preparations, or those containing salicylanilide or glyceryltriacetate. In the diagnosis and treatment of superficial dermatomycoses, as well as in tracing the source of infection when indicated, a specialist in dermatology is best consulted.

In the last 15 years the incidence of *Candida albicans* infections of the skin and mucous membranes has greatly increased in pediatric practice as well as in general medicine. In contrast to the situation with ringworm infections in which systemically administered griseofulvin has relegated local applications to a secondary role, in candida infections a highly effective material, nystatin (Mycostatin) has been developed which for all practical purposes is useful only if topically applied.

It is available in ointment and cream preparations as well as in a dusting powder, all containing 100,000 units per gram. It is water-insoluble, and in watery suspension it soon loses activity. In oral thrush of the newborn, freshly prepared suspensions can be applied to the lesions several times daily. Elsewhere, particularly in folds, the freely applied powder is the best application form. Mycostatin is truly effective only against *Candida albicans* infections.

An old-fashioned and messy but also effective antimonilial therapy is gentian violet paint, which is applied in 0.5 to 1 per cent concentration in water or in weak alcoholic solution.

The treatment of scabies has been revolutionized by the discovery of two antiscabetic compounds, benzyl benzoate and gamma-hexachlorocyclohexane, which made the application of strong sulfur ointments obsolete. These advances have been particularly important in pediatric practice, since the sulfur treatment always carried a risk of systemic poisoning.

There are several preparations of benzyl benzoate in aqueous emulsions available on the market (Zylate, Topocide, and others) and ready for use with instructions. Similarly, gamma-hexachlorocyclohexane is commercially available under the trade-mark name Kwell. Benzyl benzoate and Kwell are useful also in other cutaneous parasitic infestations such as pediculosis.

DDT in unregulated amounts is not recommended for application to the skin in pediatric practice. It is not quite safe because in the presence of organic solvents, DDT is easily absorbed and may cause systemic poisoning. On the other hand, in bedbug- and flea-infested areas it is the compound of choice for extermination on the premises.

The modern insect repellents such as 6-12, or 2-ethyl-1, 3-hexanediol are extremely useful preventives of insect bites.

The widespread local use of elementary sulfur in infections and infestations has practically disappeared in the last 20 years because of newer and more effective, less irritating drugs. Nevertheless low concentrations of sulfur (1 to 3 per cent) in dusting powders can still be used advantageously, for instance in the prophylaxis of dermatomycosis pedis (to be applied thickly to feet and interspaces of toes and into the socks after swimming or showering in public places) and of trombidiosis (chigger bites) by applying it all over the legs and lower body before walking through tall grass in infested areas. It is an inexpensive way of prophylaxis, an important point from the public health point of view.

"REDUCING" AGENTS

Originally the designation "reducing agent" was applied to substances used in topical therapy which were thought to effect chemical reduction. In this paper the term is used for those agents which reduce benign epithelial proliferation, hyperkeratosis and cutaneous infiltration as they develop in subacute and chronic inflammatory processes. These agents also often normalize faulty keratinization.

Tars are still the most important "reducing agents" in the treatment of subacute and chronic eczematous eruptions and of psoriasis.

Tars are dry distillation products of wood (pine, birch, juniper), coal (crude coal tar) and bituminous shales (ichthyol) or petroleum (naftalan).

Coal tars are most widely used in dermatology. The crude coal tars, usually prepared from anthracite coal, have an extremely complex and somewhat variable composition. Four fractions are usually distinguished: (1) the light oil fraction containing phenol, benzene, toluene and xylene; (2) the medium oil fraction containing naphtha, heavy benzene, and higher molecular phenols; (3) the heavy oil fraction con-

taining naphthalene, creosote and other liquid and solid hydrocarbons; and (4) the anthracene oil fraction containing the "green oil" with anthracene derivatives such as acridine and other fluorescent substances. All these fractions seem to be required for full therapeutic action.

The pharmacodynamics of this complex mixture is poorly understood. All we know is that it reduces abnormal epidermal proliferation (acanthosis, hyperkeratosis, parakeratosis) mainly by virtue of the anthracene compounds present, and that it has vasoconstrictor and antipruritic effects. Clinical experience indicates that the disappearance of cellular infiltrates in the corium is a consequence of the primary action of the tars in the epidermis. The prompt antipruritic action is due to the phenolic compounds in the tar, but later the "reducing" action on lichenified skin may play a major role.

It may seem paradoxical that coal tars which contain carcinogens and in general promote epithelial proliferation and hyperkeratosis are used to reduce acanthotic and hyperkeratotic processes in disorders such as psoriasis or lichenified forms of atopic dermatitis. The probable explanation for this paradox is that the tar first produces thinning of the epidermis before causing proliferation; apparently this initial phase of tar action is utilized in topical therapy.

Although there is a certain analogy between the therapeutic effects of tars and of fractional x-ray doses, the application of tars in the usual manner of therapy involves no risk of damage and particularly no danger of carcinogenesis.

Crude coal tar can be used in lotions, pastes and ointments and in some instances as an undiluted varnish. The concentration chosen depends on the severity of epidermal thickening and dermal infiltration, and on the irritability of the lesion. It can be used in from 1 to 100 per cent concentration. Its main indications (in combination with ultraviolet irradiations) are psoriasis and dry forms of atopic dermatitis. Many pediatricians and dermatologists find that tar preparations are well tolerated even by infants with the more exudative forms of infantile eczema. Good tolerance and excellent effects are indeed sometimes amazing.

Local undesirable side effects may be folliculitides, due to occlusion and irritation of pilosebaceous units ("tar acne"), and acute inflammatory irritations. Both complications require temporary cessation of tar therapy. If higher concentrations are applied to large areas, urine analyses should be done at regular intervals because of the possibility of absorption and kidney damage. In the presence of kidney or liver disease the external use of tars is not recommended.

The highly effective combination of ultraviolet irradiations with tar applications is believed due to a photosensitizing effect of the acridine

compounds in tar, but this phenomenon has not been thoroughly investigated.

Crude coal tar preparations are rather messy, and they hardly can be applied without the use of dressings. Some modified coal tar preparations, such as Doak's tar distillate, Zetar and the alcohol-soluble liquor carbonis detergens, are less messy acceptable substitutes.

Wood tars, such as juniper tar (oil of cade) and pine tar, do not contain anthracene compounds. Still, in many instances in which tar is indicated they are even more effective than crude coal tar, but at the same time are more often irritating and, therefore, are hardly ever used in present-day pediatric practice. The same is true about a tar preparation from crude petroleum benzin called naftalan.

In contrast, the tar from bituminous shales, called ichthyol, is still among the most useful topical applications. In contrast to coal and wood tars, in addition to hydrocarbons and phenolic compounds, it also contains organic sulfur compounds from an oily residue left from fossil fish. In processing ichthyol it is sulfonated with sulfuric acid and neutralized with ammonia.

Ichthyol is a mild-acting tar with many virtues of other tars, but with practically no irritating effect. It renders excellent services in subacute eczematous processes in which there is moderate inflammation with irregular (parakeratotic) scaling and intense pruritus. It is about the best local application in infantile eczema if there is no considerable exudation. It is used in lotions and in soft pastes with dressings. The concentrations used range from 2 to 5 per cent. The best preparations are the pastes made with zinc oxide ointment (ichthyol or ichthammol 2.4 to 6.0; zinc oxide ointment USP, q.s. ad 120.0). They are applied thickly twice daily with dressings and removed, if necessary, gently with oil. Although ichthyol has the antipruritic and keratinization-normalizing effects of tars, it has not sufficiently strong tar effects for the treatment of infiltrated chronic eczematous patches.

ANTISEBORRHEIC AGENTS AND THE EXTERNAL TREATMENT OF ACNE

It was thought for a long time that the effectiveness of elementary sulfur in powders, lotions, pastes and ointments in the treatment of oleic seborrhea and of acne vulgaris is based on its counteracting sebaceous gland hyperplasia by hindering mitotic division in the basal cells of these glands. Therefore sulfur was listed as an "antiseborrheic" agent. More recent experimental work[3] indicates that this is not the case. If anything, sulfur increases sebaceous glandular volume. Its effect in acne seems to be based on a keratolytic action which relieves the obstruction of the follicular canal with hyperkeratotic masses, which is a key pathogenetic factor in the development of acne lesions.

The effect of sulfur in oleic seborrhea and its "drying action" in general remain a mystery.

Pharmacologically, sulfur acts by being reduced to sulfides when in contact with tissues. These sulfides have considerable antiseptic effects against microorganisms and animal parasites.

The often observed irritating action of sulfur seems to depend somewhat on the original particle size of the sulfur powder used. Precipitated sulfur USP, as contrasted with sublimed sulfur, is finely enough dispersed to avoid irritation in most cases. Therefore in all prescriptions sulfur is best specified as precipitated sulfur. Some authors claim that colloidally dispersed sulfur is even better tolerated and is still more effective.

In acute and subacute seborrheic dermatitis low-concentration (0.5 to 2 per cent) sulfur ointments, creams and pastes are often the treatment method of choice. In spite of its name nobody has ever shown that this condition has anything to do with local seborrhea, and its nature is still a mystery. Thus it is not surprising that almost nothing is known, either, about the action mechanism in this disease of topical sulfur applications. It seems that their anti-inflammatory effect comes about through correction of faulty keratinization and by reduction of the cutaneous microbial population.

In recalcitrant cases of seborrheic dermatitis with persistent chronic lesions (rare in children) some authors advocate high concentrations of sulfur preparations as being nonirritating and highly effective.

In adolescent acne certainly, relatively high sulfur concentrations are well tolerated. Sulfur is used in lotions, pastes and ointments, usually in 3 to 10 per cent concentration. In acne the effect of sulfur is often reinforced by the keratolytic action of salicylic acid and resorcin, and many proprietary acne preparations contain these ingredients. The main objection against the use of proprietary preparations is their fixed concentration. The discriminating physician will choose and change ingredients and concentrations according to the degree of severity of the process and will get much farther in this way. Local application of resorcin is contraindicated in cases with kidney damage.

The routine topical treatment of mild to moderately severe cases of acne includes instructions about washing, local ultraviolet light irradiations and application of sulfur-containing preparations.

Washings are preferably done with sapo mollis, usually twice daily, once in the morning when removing the night application and again in the evening just before use of ultraviolet irradiation. If signs of chappiness appear, one of the washings can be done with a milder soap.

Ultraviolet irradiations are taken at home with a Westinghouse or General Electric-RS sun lamp bulb which can be screwed into an ordinary light socket such as that of a gooseneck lamp. Irradiation to

the affected areas is given daily at a distance of 15 inches, beginning with an exposure time of one minute, which is increased 30 seconds daily up to a maximum time of 10 minutes or until mild erythema is produced. For the face, separate overlapping exposures of this sort are given to the right and left sides and to the front. The eyes are protected, preferably with moist cotton, and the patients are carefully instructed to take precautions against falling asleep under the lamp. With this method frank sunburn reaction is avoided, but a mild inflammatory reaction is created which is associated with a hardly noticeable "peeling." In fair-skinned persons, such irradiations are used only for limited periods to avoid premature aging of the skin.

In summertime the sun lamp can be put aside, natural sunshine having a much more powerful effect on acne than the artificial ultraviolet source. Patients should be advised to spend some time lying in the sun so as to get direct insolation on the affected areas. Helpful overnight applications are (1) sulfur lotions: 3 to 5 to 10 per cent sulfur in the zinc shake lotion described on page 702; and (2) in more severe cases, sulfur-salicylic acid-resorcin pastes, e.g. resorcin 1.2, salicylic acid 3.0, sulfur ppt. 6.0, zinc oxide ointment q.s. ad 60.0. In case of irritation one either discontinues this latter application for one or two nights or may decrease the concentration of constituents by adding one third of the weight of zinc oxide ointment.

In daytime, sulfur lotions with some coloring matter added may be used and are liked by girls. For instance:

Neutracolor (Almay)	5.0	(may vary from 3.5 to 8.0)
Resorcinol	2.4	
Precipitated sulfur	6.0	(may vary from 3.6 to 18.0)
Zinc oxide	10.0	
Talc	10.0	
Prepared calamine	10.0	
Glycerol	10.0	
Ethyl alcohol 95%	20.0	
Distilled water q.s. ad	120.0	

See also page 789 ff.

KERATOLYTIC AND KERATOPLASTIC AGENTS

Salicylic acid is the most frequently used keratolytic agent for the softening and removal of hard, thick, hyperkeratotic tops of calluses and warts, and also for thick psoriasis plaques and hyperkeratotic eczemas, particularly on the palms and soles. If a thick, diffusely hyperkeratotic psoriatic scalp, for instance, is shampooed daily with tincture of green soap, and subsequently 3 to 5 to 10 per cent salicylic acid in petrolatum is rubbed thinly into the scalp skin after parting the hair for 4 subsequent days, the hyperkeratotic layer disappears completely. Ichthyotic

and asteatotic, chappy skin also can be kept much smoother if the salve used contains 1, 2 or 3 per cent salicylic acid. Salicylic acid also serves as a pacemaker for other active ingredients in scaling hyperkeratotic dermatoses. In such conditions it is often admixed with tar or ammoniated mercury or sulfur, or some other agent.

If salicylic acid is applied in high concentrations (30 to 40 per cent) in an occlusive base to the skin, as is the case with corn plasters, its action may penetrate much further than the horny layer. It may exert an action on living epidermal cells, causing so-called retecytolysis.

In concentrations around 2 per cent or lower, salicylic acid ointments have a normalizing action on faulty keratinization such as parakeratosis. Probably this action represents the "keratoplastic" effect of Unna.

The keratolytic action of sulfur has already been mentioned. Probably the sulfides formed in the tissue are able to reduce the disulfide bridges in the keratin molecule, thereby disintegrating its structure.

Resorcin is also keratolytic, but its effect is more superficial, and it has no normalizing effect on keratinization. Ointments with high resorcin content cause peeling of the horny layer in thick, dark, dry pieces. In the past this effect was utilized in the therapy of acne. The application of highly concentrated resorcin preparations has become obsolete, however, particularly in children and adolescents, because of the danger of systemic absorption. Both salicylic acid and resorcin also have antimicrobial action.

ANTIHIDROTIC AGENTS

Localized forms of hyperhidrosis, if not too severe, are locally best treated with dusting powders. A relatively strong, but by adolescents well tolerated, dusting powder for the soles is powdered tannic acid, powdered boric acid and zinc oxide. In infants and small children hyperhidrosis and complicating heat rashes (miliaria) are best treated with nonmedicated powders such as the spermaceti powder, mentioned on page 701.

Axillary hyperhidrosis in adolescents may become a clinical problem. Local use of aluminum hydroxychloride preparations is the treatment method of choice. They probably act when effective as mild irritants and as such cause plugging of the orifices of the sweat ducts. If commercial preparations are recommended, it should be ascertained that no other possibly harmful active ingredient (for instance those zirconium salts which cause sarcoidal reactions) is contained in the particular brand. Malodor can be counteracted by antibiotic powders or lotions.

Adolescent boys may have embarrassing, intense hyperhidrosis of

the soles which often is malodorous (bromhidrosis) and cannot be successfully combated by astringent dusting powders. Formalin, 0.25 to 5 per cent in 50 per cent alcoholic solution painted on once daily or every other day for a week or so, may help without unduly stiffening the horny layer.

Needless to say, in addition to topical applications much else can be done to alleviate hyperhidrosis and its complications. In prickly heat of babies air conditioning is by far the most effective treatment method. In serious cases of hyperhidrosis of palms and soles of adolescents, modern anticholinergic drugs such as Probanthine are highly effective. If dripping hyperhidrosis persists beyond puberty, sympathectomy might be considered.

CONCLUDING REMARK

In this limited presentation, of course, it has been impossible to cover all aspects of the vast subject of topical therapy. Rather, an attempt was made to select for consideration particularly those points which in the authors' experience and opinion are likely to have most interest or significance to those who deal with pediatric skin disorders.

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PSYCHOLOGIC CONSIDERATIONS OF THE SKIN IN CHILDHOOD

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Today there is little question about the role of emotional factors in some diseases of the skin of adults. The position of emotions in the causation and influence of skin diseases of children is less certain. We believe that there are important emotional factors in all patients with skin diseases in childhood as well as adulthood. In some patients there is a primary or causal relation; in other patients the emotional factor is a secondary one arising out of the meaning of the skin changes.

Slowly but surely, concepts of the role of emotions in changes in the function and structure of bodily organs have evolved. Generally emotional influences have been understood sooner by poets and philosophers than by physicians. Consequently we see many literary references to these influences at a time when medicine was absorbed in considerations of morphology and organic pathology. There were exceptions: Plato warned of the dangers of separation of the soul from the body; Hippocrates invoked, "Physician, heal thyself," thereby recognizing the influence of the doctor-patient relation; Democritus wrote an essay "On Those Who Are Attacked with Cough after Illness." Zilboorg points out that from A.D. 200 with the death of Galen the dark age of medical history began. It was not until the sixteenth century that medicine began to recover. The work of Stahl (1660–1734) stands out in the history of psychologic medicine. He recognized the effect of "passions" and "affects" on the body and believed that emotions might interfere with the recovery from a physical disease. Hack Tuke published a series of articles in 1870–72 under the title, "Illustrations of the Influence of the Mind upon the Body in Health and Disease."

Turning to the skin in particular, it is interesting that Tissot (1750–1826) believed that tickling in evoking the emotions of cheerfulness and laughter had a curative effect in children suffering from rickets. Erasmus Wilson's description[15] of neurotic excoriation on the face of a 47-year-old maiden lady in 1874 is perhaps the earliest description of a purely psychocutaneous disease. She is described as "a decidedly nervous person, shy, silent, dejected, occupied with her inward self, and desirous of shunning observation." She volunteered that "the lesions were initiated by a feeling of fulness, burning, tingling, prickling and itching," and in general she had "no peace of mind until she had rubbed them or scratched them and produced a flow of blood," in which case the uneasiness ceased.

Besnier[1] in a classic description in 1892 showed appreciation of the emotional component in atopic dermatitis. He remarked that the disease becomes a unique property of the individual, a "pruritic diathesis."

Although Vidal originally described lichen simplex chronicus, it was Brocq[3] who fully realized the psychosomatic implications of the disease and renamed it neurodermatitis circumscripta. In reporting nine patients with the disease he observed that the one thing which especially seemed to dominate in these cases was a decided nervous condition. "Sometimes it consists of a simple impression-ability, keener than that of the great majority of persons; sometimes it is a very pronounced tendency to fly into furious rages for the most trifling reasons, and even without reasons; sometimes he has a predisposition to cry for the least cause, to have gloomy ideas, sometimes it is a true neurosis well characterized by nervous crises. Hysterical choking sensations, hemianesthesia, attacks of hysteral epilepsy etc."

In addition to these early observations on the role of the emotions with function and altered structure of the cutaneous system, the role of emotions in causalgia, urticaria, acne, palmar hyperhydrosis, delusions of parasitosis and rosacea have been well documented in the dermatologic literature.

But whether dealing with the skin or the patient as a whole, medicine was far from any effective approach to the mind-body problem. It was not until the second psychiatric revolution at the outskirts of the twentieth century that the more familiar, contemporary trend in dealing with this problem had its beginnings. Although from the turn of the century there has been increasing awareness of the interrelation of the skin and the psyche in health and disease, the exact nature of that interrelationship and how to use any available knowledge clinically have been uncertain. It is the purpose of this paper to emphasize some present psychiatric knowledge and how it relates to dermatologic patients. A classification of emotions in dermatologic practice

will be given. Clinical examples of cases of atopic dermatitis, trichotillomania and congenital ichthyosis will be used to illustrate the classification.

A number of beginning studies of psychocutaneous relations have been made.

English[4] listed the eight most common emotions causing skin disorders as the need for love, anxiety, hostility, inferiority feelings, ambivalence, guilt, ambition and envy. Wittkower and Russell[14] briefly describe 12 ways in which the skin may be influenced by the mind. Brandt[2] in 1950 offered a classification of emotional influences in skin diseases. He presents nine different psychosomatic mechanisms, including such concepts as nonspecific mental elicitation, sensory neuroses, and involvement of the skin by detour, as well as the more common concepts of direct damage to the skin by neurotic acts and skin disorder as a conversion phenomenon. There are numerous case reports and discussions of itching and scratching. Although each has its useful place, it has been difficult to integrate many of these concepts into an approach to the patient.

Regardless of the etiology of the disorder, there are emotional considerations in all dermatologic patients for several basic reasons:

1. Man is a social organism and cares what others think of him.
2. The appearance of the surface of the skin has meaning in terms of a person's self-esteem and feeling of acceptability to others.
3. The skin is a perceptive-protective barrier which informs the individual of, and protects him from, the external environment. Any change in the surface of the skin inevitably has emotional significance because its occurrence is a potential threat to the performance of vitally important functions.

Consequently all skin patients will fit into one or more of the groups *primary*, *secondary* or *collaborative* (Table 1). As might be expected from the term "primary," this group contains those cases in which the primary problem is an emotional disorder which uses the cutaneous system as part of its expression. This would include trichotillomania, factitial dermatoses, psychotic delusions, neurotic excoriations, lesions secondary to compulsive symptoms, phobias, some cases of pruritus, dyshidrosis, urticaria, rosacea and localized neurodermatitis. Some cases of alopecia areata, lichen planus and atopic dermatitis may also be included. The origin of the symptoms being emotional, the major treatment problem is a psychiatric one. The cutaneous lesions need care, but their prevention or removal is primarily dependent upon treatment of the emotional failure.

All dermatologic patients fall into the secondary group because of the three basic reasons stated above. Nevertheless we should like to emphasize that this includes not only dermatologic patients of the

TABLE 1. *Classification of the Role of Emotions in Dermatologic Practice*

Primary	Includes all skin diseases which are the direct result of emotional conflicts. In these disorders there is a primary involvement of the personality, with selection of the cutaneous system as the target or site of expression
Secondary	In all skin diseases there is inevitably an important emotional impact. Changes in sensation and appearance have meaning for the patient. Directly and indirectly these influence feelings about himself and may influence his relations with others. The age of the patient and the nature and location of the lesion are important variables
Collaborative	In many skin disorders there is an interplay of factors which have varying importance. These disorders may range from the situation in which the emotional factor is so heavily weighted that the treatment should be primarily psychiatric to the situation in which the treatment should be primarily dermatologic. Between these 2 extremes are many patients who require both dermatologic and psychiatric treatment

primary type above and those in whom there are multiple etiologic factors, but also those patients whose skin problem is clearly due to an infectious, congenital, allergic, toxic or any physical cause. Even when the major cause or causes of the skin problem are organic, the secondary emotional problems may well be the most serious interference with the patient's life adjustment and even a threat to his life. Case 2 (p. 731) is an example. This case points out the additional factor that when the patient is a child, the skin disorder not only can cause faulty emotional functioning, but also can interfere with the development of the underlying mental structure. There are a number of variables which influence the impact of a skin disease on the patient, regardless of the initial cause. These include (*a*) the extent, duration, location and nature of the skin disease; (*b*) the past life history of the patient with special reference to (1) the meaning of skin for that individual, (2) the meaning of skin in that family and cultural group, (3) the meaning of illness in general, and (4) the meaning of skin ailments in specific; (*c*) the time in life when the lesion occurs; (*d*) the capacity of the individual for toleration of stress at that time.

Despite the advantageous position of the skin for observation of emotional influences upon an organ system and despite early recognition[4] of the importance of emotional factors in skin diseases by Wilson, Besnier and Brocq, progress in this area has been slow. We feel that in part this is because (1) there is a tendency of the physician to refer the patient to a psychiatrist and drop out of the picture or to overlook the importance of the emotional etiology in patients in the

primary group. The patient is often not convinced of the emotional nature of his skin problem and in order to seek and follow through with psychiatric help needs the sustained interest and firm stand of the referring physician. Both physicians need to treat and study these patients jointly in order to learn how to treat them more effectively.

2. There is a large gap between the available technical knowledge of personality functioning in the psychiatric specialty and the level of absorption of this knowledge by nonpsychiatric physicians. This gap is in part a problem of communication.

3. Even when important psychophysiologic and psychopathologic relations have been discovered in individual cases, this knowledge has not been forged into a general body of knowledge with which to approach dermatologic patients as a group.

Perhaps there has been a greater attempt to correlate knowledge of psychophysiologic and psychopathologic relations in our collaborative group of patients because here the response to the treatment of the dermatologic symptom by the same method varies according to the degree of the emotional component in the illness. It has long been apparent to us and to others that there is considerable emotional interplay in some children with atopic dermatitis. We have chosen a case of atopic dermatitis to illustrate this group (see p. 733). Nevertheless it is not enough to confine the study of emotional interplay to the collaborative groups, because in our studies of alopecia areata, atopic dermatitis, psoriasis, acne and urticaria the impact of that interplay is often superimposed upon or added to the basic meaning of the skin and illness for that patient. Moreover, when the illness has started in infancy or childhood, the presence of the illness in the developmental period inevitably results in an absorption of the skin condition in the individual's concept of himself and his mechanisms of interacting with his internal and external environments. It is because of this that we have evolved our classification and feel that an important starting point for all who are interested in the treatment of patients with diseases of the skin is the understanding of the meaning of the skin for that individual. Children provide us the opportunity to make observations before long and complex interrelations have developed. There is a responsibility in the treatment of children to minimize so far as is possible the interference with normal emotional development that a skin disorder often causes.

The effective use of this classification requires considerable psychologic understanding and implies the clinical usefulness of such concepts as (*a*) the growth and development of the mental apparatus; (*b*) the meaning of the skin as an organ system; (*c*) the meaning of illness; (*d*) the functional interrelations between the skin and the mental apparatus in health and disease; (*e*) the importance of collaborative

efforts between the physician initially seeing any patient with a skin lesion and the dermatologically oriented psychiatrist. This is necessary for the furtherance of our theoretical understanding as well as for the most effective treatment of many patients.

DEVELOPMENTAL CONSIDERATIONS

Man is the result of centuries of evolutionary development from unicellular forms of life to a complicated, multicellular, multiorganed organism. His phylogenetic heritage is represented at birth by the genetic representation of potentials for the development of the means with which to cope with his internal and external environments. The task of the newborn is to take the sum total of potentials with which he arrives in life and to express these in such a way that he finds satisfaction and can grow and develop toward adulthood and the reproductive maintenance of his species. In doing this, he must protect himself from the dangers of the physical environment and avoid conflict with others.

The impetus toward growth, development and interaction is represented in what are called the instincts or instinctual drives. In terms of mental structure these are often called the *id*. To aid in dealing with the demands of the internal impulses and the outer world it develops an administrative apparatus, the *ego*. The ego develops various mechanisms with which to carry out its task. Living in a complex society, man must control his strivings not only in the presence of other people, but also in their absence. To this end, he evolves an agency which is the internal representative of other people's dictates, the *super-ego*. A part of the super-ego coincides with what we know as the conscience. This total mental structure influences and directs bodily functions in the interest of the total organism. It is not present at birth as an integrated whole, but begins to evolve in the early weeks of life. The body that it is later to influence and control plays a very important role in the development of the mental apparatus.

Since the human infant is born in an undeveloped and helpless state, he must have an intermediary to perform many of the steps in the maintenance of his life until he is capable of carrying on these functions for himself. These are carried out by the mother. Spitz[12] views the mother as a substitute or external ego and points out that the somatic and psychic systems of infants are not separated during the first six months of life. In a passage of particular interest to pediatricians and dermatologists he states: "In the process of psychological development in the course of the first year of life the child acquires its ego with the help of numberless identifications with the mother

which are made possible through the *Sensory Experiences* offered by her. Among the most important of these, if not the most important, are the *Tactile Experiences,* which include both superficial and deep sensitivity" (italics added).[13]

Further than this, it should be pointed out that the whole of psychoanalytic theory of child development revolves around the concepts of erogenous zones which, by means of the heightened capacity for stimulation, play a vital part in the psychic development of the child. These areas include progressively the mouth area, the anorectal area and the genital area. The erogenous zones are only special areas of the cutaneous system as a whole. Both the cutaneous system and its special zones play a vital role in the development of mental apparatus, and it behooves anyone interested in the function of the mental apparatus and the organism as a whole to pay particular attention to the skin as an organ system. Conversely, it behooves anyone who is interested in the cutaneous system to be interested in the evolution and function of the mental apparatus.

THE SKIN AS AN ORGAN SYSTEM

The skin is a sense organ, a protective interzone, and an organ of expression. It serves important physical, biochemical, physiologic and psychologic functions. It is an adaptive organ par excellence, which perceives outer and inner environments and responds to each.

As a sense organ with its special receptors for heat and cold, pain and touch, it has capacity to inform not only itself as an organ system, but also the organism as a whole. The capacity of the skin as a sense organ is intimately connected with its functions of protection, gratification and expression.

The *protective function* of the skin includes protection against traumas, temperature change, fluid loss, bacterial and viral invasion, and light absorption. Less frequently described are the psychologically important functions of (1) protection against too many incoming stimuli,[6] whether painful or excitatory; (2) protection against the loss of the sense of reality. Recent isolation and sensory deprivation experiments[8] indicate that a constant flow of sensory stimuli serves the ego in the maintenance of its sense of reality.

The *perceptive functions* of the skin are useful to the organism not only in protection from physical damage, but also for the regulation of the amount of incoming stimuli, so that this will be a source of *gratification* and not one of frustration. From birth onward the skin is an important medium through which gratification is received. In infancy and childhood these functions play a role in the development of the psychic apparatus; throughout life contact with others and

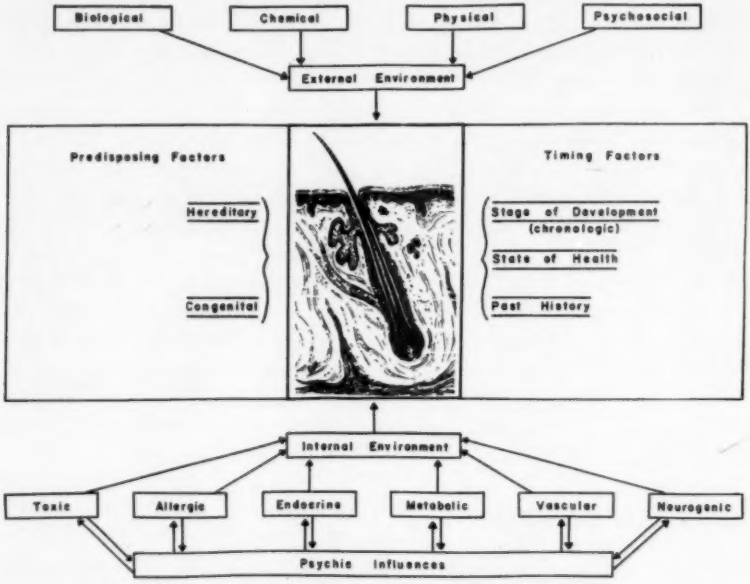

Fig. 6. Factors affecting the structure and function of the skin.

gratifying stimulation through the skin are a necessary part of healthy life adjustment.

Finally, the skin has an *expressive-communicative function*. Through qualitative changes in the appearance of the skin the feelings and affects of the person are revealed or conveyed to others. Hecht[5] mentions the following ways in which the skin is a medium of communication: (*a*) communication of emotion, e.g. blushing with anger, shame and excitement; (*b*) arousal of emotion, e.g. through a beautiful or repulsive complexion; (*c*) the recipient of emotion, e.g. being touched, pinched or beaten; (*d*) as a carrier of emotional meaning (for one's self), e.g. reflection of feelings of health and self-respect versus feelings of ill health and lack of self-respect.

From the foregoing discussion and the considerations of psychic development, it can readily be seen that there are similar functions of the skin and the ego. This is not surprising, because observation of phylogenetic development readily reveals that prior to the development of a nervous system the organism was informed by its surface covering, and the primary zone of interaction was at that surface. As organisms became multicellular and multiorganed, the surface covering continued its functions of interacting and informing, but these became to a degree subservient to the integrating and administrative

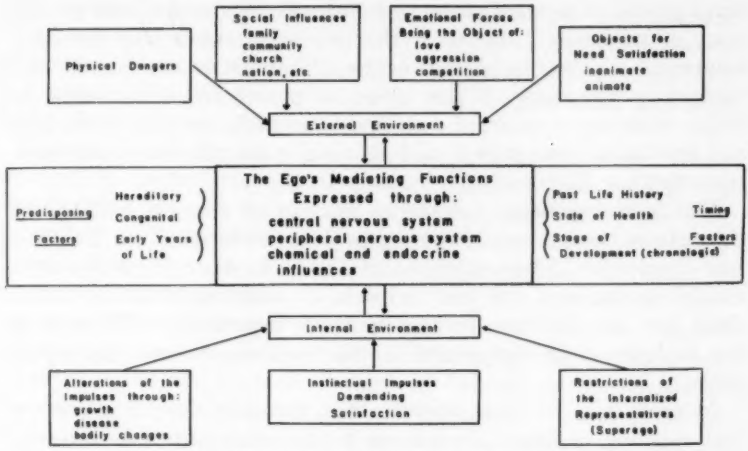

Fig. 7. Factors affecting the development and function of the ego.

apparatus of the organism. In man the integrating and administrative apparatus is the ego. Ego function depends upon an intact central and peripheral nervous system. It is therefore also not surprising that embryologically the skin and the nervous system have a common ectodermal origin. The functions of the skin and the ego are so similar in many respects that we have compared the factors affecting the structure and function of the skin (Fig. 6) and the factors affecting the development and function of the ego (Fig. 7). These demonstrate the similar functional position and similar factors involved in the development and function of the skin and the ego.

The interrelation of the functions of the skin and the ego is so close that in the life history of each person the meaningful experiences inevitably give meaning to the skin as a whole and to specific areas of the skin. Especially when this meaning has particular significance or when there has developed a hyperresponsiveness or hyporesponsiveness, it will play a role in the occurrence and type of skin disease.

THE MEANING OF ILLNESS

The growing child, like every other human being, is continually trying to orient himself to his inner and outer environments. A person's body not only provides the equipment with which that orientation takes place, but also is part of the environment. The child's task is complicated for several reasons: (1) His body is constantly changing in size and shape. (2) There are qualitative changes in terms of successive

development of new capacities and in terms of changes such as take place at puberty. (3) He is in the process of developing the same equipment which is to be used in the adjustment to the internal and external environments. (4) This process of growth and development includes becoming acquainted with one's own body, gaining a structural and functional concept of it, and accounting for differences and variations that are discovered.

This basic experience establishes concepts of the self, others, and the external environment which provide a background for handling new experiences. The occurrence of illness at strategic periods of a child's development not only imposes an additional burden on the child, but also threatens to alter basic life experiences which will be the background of comparison for the handling of new life experiences.

At each stage in every person's life experience there is a concept and meaning of illness. In infancy it can mean little but increased frustration at a time when frustration is poorly tolerated. Later, it may represent fear of (1) pain, (2) being different through bodily alteration. Later, this is more firmly established as castration fear. (3) Loss of control of one's body, of being ashamed; (4) separation, especially when hospitalization has previously been involved. In older children there may be fear of death. (5) Loss of love, especially when there is a change in bodily appearance.

Skin eruptions present a special problem because they can be seen by one's self and by others. There is increased concern about the bodily appearance and the need to account for the changes in some way. A reversal of this problem is seen when healthy children paint on spots so as not to be different from the child who has measles or when a child wants to simulate the appearance of the parent who has a skin disease.

Although at each stage of life there are some general considerations of the meaning of illness, there will be considerable variations in terms of each person's life history. This makes each case an individual one and makes the practice of medicine a continual challenge even in cases of the same illness.

INTERRELATION OF THE SKIN AND THE PSYCHE IN SKIN DISEASE

Because there is a developmental and functional interrelation of the skin and the psyche from birth onward in health, there is an inevitable relation in disease. The time of onset of disease is of the greatest importance, as is the past history. There is variation in the meaning of the skin, of illness, and in the tolerance of stress. An infant may be overwhelmed by the increased frustration associated with

skin disease. If the frustration is severe enough, it may also interfere with psychic development. The result is a demand for greater maternal protection. The two- to three-year-old child may be concerned with the control of bodily sensations, with bodily appearance, and with bodily differences and dirtiness.

Anxiety may be expressed over the eruption, or the eruption may be used to control the parent through demands and itching and scratching. A four- to six-year old may be embarrassed by the rash, the itching or the scratching. He might also obtain considerable gratification from it. A preadolescent child might become the brunt of teasing and nonacceptance. An adolescent might have a serious lowering of self-esteem with an eruption or might completely deny concern and refuse to be treated at all. Each child brings many special considerations. The best manner in which to demonstrate the relation of the skin and psyche in disease and to illustrate the clinical usefulness of the classification of the role of emotions in dermatologic practice is through some typical case histories.

Primary Interrelation

The first case is that of a 10½-year-old boy with trichotillomania. We were consulted by the child's parents because of patchy hair loss on the scalp of nine months' duration which the family physician said was due to a "nervous condition." The father observed that his son pulled his hair, was shy and nervous, and had difficulty in school.

The hair loss first appeared shortly after his mother went to work. Significant facts in the past history were as follows: he had a tonsillectomy at age two. At age 3½ the first of several consecutive patches of alopecia areata appeared on mother's scalp. He did not speak clearly until he was five years old. Regular enuresis did not stop until age six after a five-week period of hospitalization for plastic surgery following a burn; thereafter enuresis occurred only with illness. Achievement in school is poor, and he was placed in a "special class." He is reluctant to touch anything which he considers dirty.

There were ill-defined patches of broken-off hairs in the frontal and temporal areas of the scalp. Some of the hairs within the patch were broken-off stubble, but some were of normal length. The skin of the scalp was normal, and the hairs in the involved areas and uninvolved normal areas of the scalp resisted epilation normally. Direct examination of hairs showed no evidence of congenital abnormalities or of dermatophytic infection.

Discussion. Trichotillomania is an emotional disorder in which the hair becomes a target of expression (Fig. 8). This case will represent the primary group in our classification.

There is indication that the tonsillectomy at the age of two years and the burn at age six years were traumatic experiences. At age four his mother described an isolated incident in which there was an unusually strong anxiety reaction when she went out for a short walk. There had been a very close relation with the mother, and one wonders what influence the mother's alopecia areata has had on the

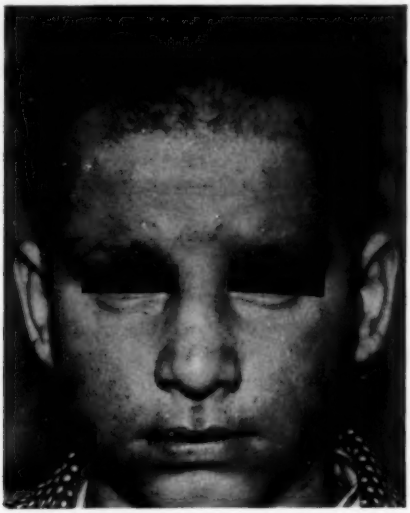

Fig. 8. Trichotillomania in a 13-year-old boy with atopic dermatitis who has excoriated and lichenified skin and manifestations of severe behavior problems.

development of the patient's trichotillomania. In addition to his symptoms and his mother's loss of hair, his drawings (Fig. 9) indicate a special significance of hair.

The anxiety with separation, the enuresis, the delayed speech, the learning difficulties, as well as the excessive concern about dirt, are indications of this child's neurotic difficulties. Although the dynamics of this case have not yet been worked out in intensive psychotherapy, his symptoms and the study of other cases of trichotillomania suggest that the hair-pulling is representative of a displaced interest in and concern about other parts of the body. It is of particular interest that this boy associates the onset of loss of hair with the hospitalization for the leg burns, although the parents report that this is not true. The burns were the result of playing with matches, a forbidden activity over which he felt guilty. There is great likelihood that the hair-pulling simultaneously represents a substitute for other bodily manipulation and a punishment for the "forbidden activity." This has been demonstrated in another case. Treatment must consist in bringing to consciousness the unconscious meaning of and need for hair-pulling. Simultaneously, it will be necessary to help him develop more effective means of handling his emotional conflicts.

This child demonstrates the absolute indication for psychiatric help. To treat this youngster locally by close cropping of the hair so that he cannot pull it or covering the scalp with an occlusive dressing must be strongly condemned. Successful psychotherapy for the under-

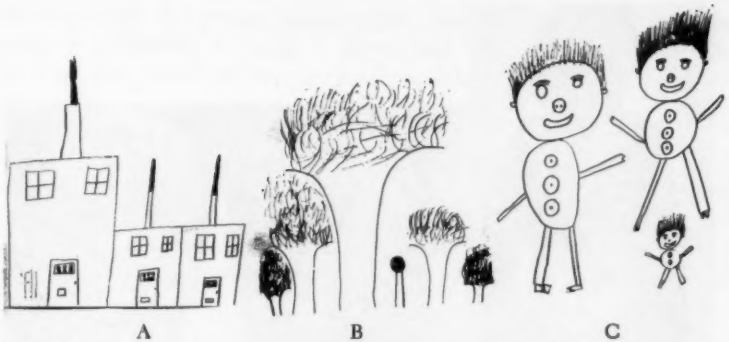

Fig. 9. Drawings of a house (A), a tree (B) and a person (C) by a 10½-year-old boy with trichotillomania, illustrating the preoccupation of the child with erect hair.

lying emotional problems will clear the cutaneous manifestations of the stress without need for local treatment.

Secondary Interrelation

Our second case is that of a 5½-year-old boy with congenital ichthyosiform erythroderma. This child is representative of those cases in which the skin problem, from whatever cause—infection, trauma, allergy or congenital defect—becomes either the cause of emotional disturbance or the focus of emotional conflicts of the child or the parents. As was indicated in the classification, the skin has emotional significance, and *all* patients with skin problems inevitably have some conflict over the skin involvement. This conflict or anxiety is handled with varying degrees of success or failure. In some cases the failure in adjustment which results from the emotional complications becomes the major problem of the patient and the major task in treatment by the attending physician.

The child, conceived out of wedlock, was born in a forced marriage to a mother of Roman Catholic background. He has had congenital ichthyosiform erythroderma since birth (Fig. 10). His mother has continuously sought a "cure" despite attempts to help her to accept more realistically her child and be able to carry out therapeutic measures at home. Repeatedly, the skin becomes worse, secondary pyoderma develops, and hospitalization is necessary. In the hospital the child promptly responds to the treatment that had been recommended at home.

The mother comes from a rejecting home and was in constant conflict with her own mother. She was three-months pregnant when she married. She was resentful of the pregnancy and of her husband's statement that he probably would not have married her had she not been pregnant. Since the child's birth she has reacted to his skin condition with crying, depression, and turning her head away. From the time the child was three weeks of age the mother worked and the child was cared for by a number of different adults. She is a domineering woman, who was conscious of death wishes early in her child's life. Her hostility and subsequent guilt and need for punishment have caused her to (*a*) deny constantly the nature of her child's illness and to seek new physicians and new treatments, (*b*) oppose physicians, (*c*) have difficulty in carrying out treatment plans, (*d*) unconsciously seek punishment through having a sick child as a burden to bear for her premarital conception and subsequent hostility toward the child.

The child's reaction to the illness is characterized by denial of the true impact of his skin disorder even though he cries about people calling him dirty and children refusing to play with him. Beyond the denial there are other problems: (*a*) he is very bashful, nonboyish and fearful of being hurt; (*b*) he is extremely sensitive to criticism;

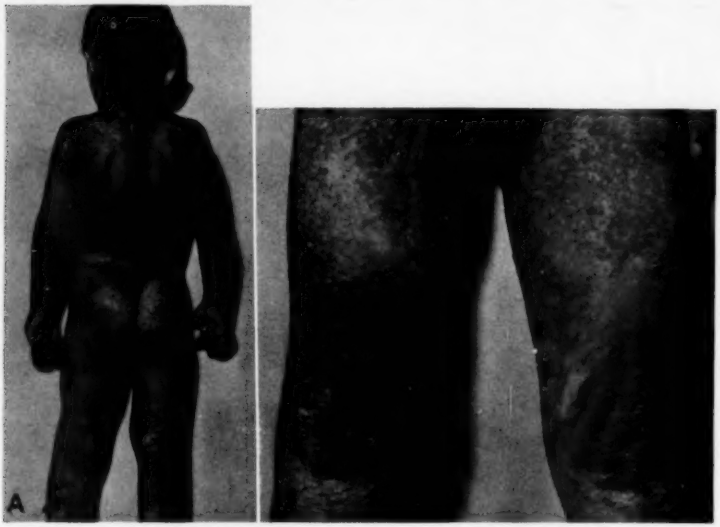

Fig. 10. Congenital ichthyosiform erythroderma in a 5½-year-old boy with a congenital disease of the skin which has secondary effects on his emotional growth and development.

(*c*) he is preoccupied with thoughts of children becoming ill and dying; (*d*) he cries in his sleep most nights; (*e*) at five months, after hospitalization and a skin biopsy, he lost weight and became a picky eater; (*f*) he even cries at discussion of hospitalization and separation from his mother, upon whom he is quite dependent; (*g*) his father's open rejection of him has been repressed, but is operative in his feelings that come out in nightmares and daydreams.

Discussion. This child with a severe congenital skin disease suffers mainly from the secondary effects of the disorder and from the meaning the disease has for his parents. Already there are signs of these secondary effects. (1) There is an overdependency on his mother growing out of (*a*) the insecurity secondary to her ambivalence; (*b*) the separations at an early age through mother's working and his hospitalizations; (*c*) mother's unconscious need to have him a sick and dependent child. (2) There is a lack of his own self-esteem as seen in his shyness, reticence and dependency. This is fostered by his parents' rejection of him and his own feeling that his skin is dirty and that he is less acceptable than others. (3) There is excessive use of denial of his lack of self-esteem, sensitivity to criticism, and anger toward his parents. This extends to other areas and interferes with his reality testing and general effectiveness. (4) There is repression of his hostility because he has not developed adequate modes to handle it. He can act only as if it does not exist. (5) Already there seems to be interference with his active masculine development. He is inclined to regard himself unconsciously not only as undesirable and

dirty, but also as a passive, unacceptable female. (6) Finally, his whole mode of responding to others is developing into a fearful, dependent, sensitive and retreating fashion. He is unable to handle his aggressive feelings and is thus deprived of the assertiveness necessary to complete or master any problem, even in learning.

Not only does this child have to contend with his own troubles, but also he and his skin have been incorporated into the expression of the needs of the parents for self-punishment. Both factors are shaping the development of his whole psychic structure and threaten to have implications vastly more far-reaching than the function of the skin.

Collaborative Interrelation

This is a case of a six-year-old boy with atopic dermatitis.

Atopic dermatitis is felt to be a disease with a number of etiologic factors. The nature of the skin and its responses are important. The emotional factor also is important in the etiology and in the treatment.

The mother stated that a dermatitis first appeared on the youngster's cheeks shortly after birth. The dermatitis progressed, and he was started on a milk substitute. Slowly thereafter the dermatitis cleared and remained clear until he was 4½ years old, when it recurred. Thereafter a persistent, extremely pruritic dermatitis defying allergic and dermatologic control remained on the face, arms and legs.

Excoriated, lichenified, erythematous scaly plaques on the face and flexural surfaces of the arms and legs were observed on physical examination (Fig. 11). The femoral and axillary lymph nodes were enlarged but nontender.

As an infant he had a rash simultaneously with feeding difficulty. When a compatible formula was found, the rash cleared. At the age of 13 through 16 months the patient would rock himself to sleep. He banged his head at 2½ years. His speech was slow in developing and for a long while was not distinct. At 2½ years of age he was very sick with mumps, having a temperature of 104° F. for 2 days. At the age of three he had a tonsillectomy because of large infected tonsils. At this time a younger

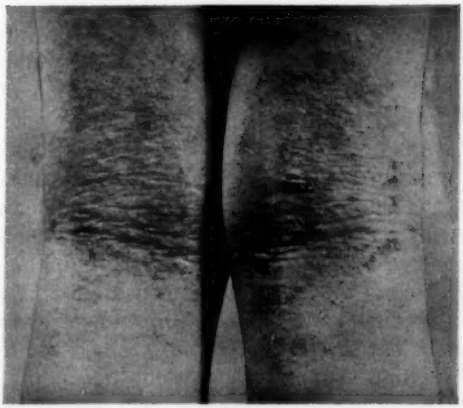

Fig. 11. Atopic dermatitis in a 6-year-old boy, showing lichenification on flexural surfaces of the legs in response to constant rubbing and scratching. This child's skin illustrates collaboration of the emotions in the pruritic diathesis.

brother was born. At 5½ years he became frightened upon being hospitalized and receiving a series of "needles." Subsequently he has been frightened of hospitals. At the age of 5¾ years he began first grade with no previous school experiences. He disliked it from the first, but is "commendably well behaved." Although he does good work, he says it is hard. He does not bother with other children at school, and he plays inside after school. His mother has noticed that he scratches longer and more intensively when upset, more when things do not go his way, more when watching television, when picked on by other boys.

When his mother goes marketing, he always expects her to bring him something and is upset if she does not. Generally, his development proceeded normally, except for his speech, which was indistinct for a number of years. His speech was of the babyish type; i.e. he said, "wide" for "ride," "pather" for "father," "cool" for "school." His mother said, "He is a very nervous child because of his skin condition."

Upon psychiatric examination the child was a pleasant-appearing blond, blue-eyed boy. His eruption was as described. These additional findings stood out: (*a*) The babyish speech persists. (*b*) He gives a "little man" appearance, which belies strong inhibitions and fear of disapproval. (*c*) He is unusually vague in many of his concepts and in discussion generally. (*d*) As was seen in his general behavior, his drawings indicated a great deal of immaturity. His concepts and structures were simple for his age group. His drawings of people indicated a good deal of distortion of male and female body images. There is little indication of feminine differences, and, interestingly, he omits the mouth from a drawing of mother.

This child is now just over seven years of age. He still shows signs of his immaturity. There is a poor social adjustment. School is difficult for him. It has been necessary to hospitalize him for an outbreak in his eruption for the third time in the last two years. It is interesting that, although present, his skin eruption was not troublesome until about 4½ years of age.

Discussion. In 1940 Pearson[10] pointed out that the emotional difficulties of a patient with an inflammatory skin condition may affect the skin lesion in 2 ways: "(1) An organic skin lesion may be increased or its healing delayed by a person's behavior towards it; (2) an inflammatory lesion may develop as an attempt to solve a difficult emotional problem." Although his cases were not those of atopic dermatitis, he points out two ways in which emotional factors are involved in atopic dermatitis, as well as other dermatologic conditions.

Kepecs et al.[7] studied 20 cases of atopic dermatitis and found that they fell into two psychologic groups. The larger group consisted of patients who were emotionally labile, had frustration of heterosexual impulses and tended toward hysteria. The other group consisted of rigid, compulsive patients. Itching and scratching seemed to be manifestations of anger at mother figures or heterosexual objects.

Schur,[11] in an excellent paper on the emotional aspects of skin disorders, presents a case of atopic eczema. The relation between the function of the ego and the outbreaks of the eruption is elucidated. Emphasis is laid upon the ego's ability to neutralize aggression.

In our case of the six-year-old boy with atopic dermatitis it is interesting to point out several aspects: (*a*) He had the first episode in infancy with clearing, except for persistent traces. (*b*) He had, and still has, a dependent relation with his mother. He makes unreasonable demands on her and is oblivious of the needs and desires of his

brother and sister. Mother and father have not been able to handle this. (*c*) Despite mumps, tonsillectomy and adenoidectomy, and the birth of a sibling, the patient did not have a severe skin problem again until he was into the Oedipal phase of development, at which time mother is no longer an object of dependency, but becomes a heterosexual object. (*d*) There are obvious signs of inhibition of his social and emotional development. His delayed and babyish speech, his isolation from others and his "little man" behavior indicate areas of problems and of poor ego growth. (*e*) He is easily frustrated and has an outburst of anger when disappointed. (*f*) There is anxiety with separation from mother. (*g*) His scratching can readily be correlated with situations of emotional significance.

This boy bears out the observations of Pearson, Kepecs and Schur. He reacts to an internal developmental conflict with his eruption (other factors are present too). Externally, the scratching with emotional tension perpetuates the eruption. He is rigid and shows poor ego development, particularly as the demands increase with his development. He seems to be ever ready to retreat to a more infantile pattern with insatiable demands on his mother and poorly controlled aggression when frustrated.

Many factors are involved in this boy's problem. He and his skin need the dermatologist's help. His emotional development is impeded, and he needs the psychiatrist's help. The skin problem and the developmental problem are interrelated, and successful treatment depends upon successful collaboration of the dermatologist and the psychiatrist, as well as the cooperation of the patient and his parents.

SUMMARY

The interrelation of the skin and emotional development and function has been discussed. A useful classification of the role of emotions in diseases of the cutaneous system has been presented.

The treatment of the patient with a severe skin disease over a long time is a many-faceted and highly complex problem which requires many kinds of skills. When the patient is a child, we are particularly concerned with the delicate and vitally important balance the patient maintains with his outside and inside environments. The skin ordinarily plays an important part in maintaining that balance. When the skin is altered, there is inevitably a threat to the organism as a whole. There is immediately a twofold problem: the care and treatment of the skin, and the observation of the organism as a whole with treatment as indicated. When the patient is a child, the problem is infinitely more complicated because the skin plays a vital role in the development of that very mental apparatus that will guide the future

destiny of the child. A skin disorder has a different meaning and impact at each successive period of development. A knowledge of the psychologic problems and characteristics of those stages makes it much more possible to gauge the impact of the skin disorder and to determine when the impact becomes an important aspect of the total therapeutic problem, and, indeed, when it becomes the major problem.

ACKNOWLEDGMENT

Dr. Holter's work in the field of skin disease was begun at Hahnemann Hospital and Medical College while he was a fellow for the American Fund for Psychiatry. He is indebted not only to the American Fund for Psychiatry for his support, but also to Van Buren O. Hammett, M.D., and Herman S. Belmont, M.D., of the Department of Psychiatry for their stimulation of his interest in this vital aspect of medical practice.

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STAPHYLOCOCCAL INFECTIONS OF THE SKIN

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In the latter part of the nineteenth century the Listerian view that suppuration in wounds was caused by germs led Sir Alexander Ogston, Birch-Hirschfeldt, Hoke and others to try to demonstrate the causative agents which produced suppuration. To keep facts in proper historical perspective it should be mentioned that von Recklinghausen and Waldeyer had previously found organisms in pus from systemic infections, but it was Ogston who thoughtfully dug deeper into the problem of suppuration and first demonstrated them in a cutaneous infection.[13]

In his classic book entitled *Untersuchungen ueber die Aetiologie der Wundinfectionskrankheiten* (1878), Koch,[20] in an organized experiment, designed his study in experimental animals based on the original observations and speculations of others to show that the so-called infective processes of wounds were due to bacteria. All was not so simple, though, for just as Jenner earlier had difficulty convincing his contemporaries of the importance and the validity of vaccination, so Koch's conclusions and methods were criticized on the grounds that in the blood and tissues numerous granules existed which, when stained with aniline dyes, were indistinguishable from micrococci.[23] Pasteur also observed micrococci in pus from a furuncle and in the discharge from osteomyelitis and was able to culture the organisms in broth. In spite of the mounting positive evidence, as late as 1879 the committee of the pathologic society of London was unable to come to any decision about the role of micrococci in infection.[18] By 1880 Ogston's investigation of 82 cases of cutaneous abscesses in patients (by staining methods and the concomitant production of septicemia or local suppuration in experimental animals) decisively and convincingly proved the association

of suppuration and cocci. In this study he clearly differentiated between streptococci ("chain micrococci") and staphylococci ("grouped micrococci"), and even at this early stage he considered the possibility of the presence of nonvirulent staphylococci on the skin surface.[25]

Subsequent investigation of staphylococci following these discoveries proceeded along orthodox lines with studies on golden yellow pigment production, morphology, classification according to toxin production, serologic patterns, and finally, pathogenicity and nonpathogenicity for animals and man.

At the beginning of the twentieth century investigators were carefully studying the immunologic aspects of staphylococci in an effort to control infection in clinical practice. The discovery that antitoxic serum against staphylococci did not meet with the spectacular success which had been attained with its use in diphtheria led to the use of various antiseptics which were at best as toxic to the tissue cell as to the bacteria. At the end of the first quarter of the twentieth century the clinician would have considered himself fortunate indeed to have had available one effective chemotherapeutic or antibiotic agent to apply locally or to be given systemically to combat staphylococcal infection.

Sir Alexander Fleming's observations (1928)[16] that staphylococcal colonies around a mold were undergoing lysis, and his epoch-making discovery of penicillin were followed 11 years later by Chain and Florey's chemical purification of the agent so that systemic administration became possible. For the first time the complete control of bacterial infections with a single drug seemed possible. This optimistic outlook was tempered with the passage of time as it became obvious that though at first sensitive, staphylococci were becoming resistant first to penicillin, then to tetracyclines, as they were used indiscriminately by the medical profession. As a direct result of the general use of antibiotics for treatment and prophylaxis in hospitalized patients, it appeared that a resistant hospital strain had arisen by mutation (phage type 80/81). Consequently it became necessary to seek continually for new agents to combat the problem produced by acquired strain resistance. Although the conquest of staphylococcal disease seemed to be at hand in the mid-twentieth century, we now realize that additional knowledge of host-parasite relations, epidemiology, and antibiotic resistance is necessary before there is full realization of this goal.

It is the purpose of this paper to review the pertinent facts about the cutaneous system's relation with its bacterial environment in health and disease; to characterize the skin response to the staphylococci in both the experimental and the clinical situation, to discuss the problem of epidemiology, and organism resistance, and finally, to correlate this information with prophylaxis and treatment in the infant's and the child's skin.

BACTERIAL FLORA OF THE NORMAL HUMAN SKIN

The bacterial flora of normal skin has been a subject of interest to investigators for many years, yet in published reports on the bacterial population of the skin there is a remarkable diversity of results. Not only has the identity of the bacterial inhabitants of the skin varied greatly, but quantitative studies have likewise shown diverse results.[15] The diversity in quantitative studies is of less importance than the flora, for it is probably a function of the methods used and the fact that there is no completely valid method of determining the number of organisms on the skin.

Price [26] distinguished between the "transient" organisms which may at one time or another be found on the skin surface and the "resident" organisms consisting of relatively few types of bacteria which apparently multiply freely in the skin. All investigators seem to agree that *Staphylococcus albus* is the organism most frequently found, but there are no uniform findings regarding *Staphylococcus aureus*, anaerobic diphtheroids and streptococci reported.[15]

Evans demonstrated in aerobic and anaerobic cultures that the bacterial flora in adults is considerably different from that described in most textbooks. The average number of aerobic organisms present in the deltoid or scapular areas was 352 per square centimeter; a similar calculation for anaerobes showed an average count of 55,384 per square centimeter. There was considerable variation in the aerobe to anaerobe ratio—in nearly half of the specimens there were more than 10 times as many anerobes as aerobes, and in approximately 30 per cent of the specimens the ratio exceeded 100 to 1. He showed that there was a tremendous regional difference in number of organisms per square centimeter and that the number of organisms was dependent on the presence of sebaceous glands rather than sweat glands. This confirmed Price's observation that the sebaceous glands are the primary habitat of most of the bacteria growing in the skin. Realizing the immaturity of the preadolescent's sebaceous gland system, one would naturally conclude from these data that there must be a significant difference in the bacterial flora of the prepuberal age group as compared to that of the adolescent and postadolescent groups.

Except for Evans's study of the bacterial flora of human skin, little or no attempt has been made to distinguish between the normal flora of the skin of children and adults.[15] In studying eight children from age two to four, several distinct differences in flora were immediately apparent. Sarcina, an organism rarely encountered in adults, was predominant in the flora of four of the children. There were, in addition, a small number of gram-positive facultatively anaerobic rods, mainly spore formers, present in most of the youngsters. Small numbers of

gram-negative diplococci, probably Neisseria, were encountered on the skin of 3 children, and one child had this organism as 75 per cent of his aerobic flora. The occurrence of the streptococci on the anaerobic plates of six of the children was especially interesting, since these organisms were completely absent from all cultures of adults in this study. Identification of the streptococci proved all to be nonhemolytic with the exception of one alpha hemolytic organism from one of the children. Another strain from the same patient was found to be a strict anaerobe, whereas all the remaining ones were facultative. It was pointed out that the failure of these organisms to appear on aerobic plates may well have been due to the antagonistic effects produced by the gram-positive rods and Sarcina.

Lovejoy and Hastings[21] first noted the presence of anaerobic diphtheroids in the sebum expressed from sebaceous glands in the normal skin around the nasal fold. The striking absence of propionibacterium acnes therefore in children with vestigial sebaceous glands is not particularly surprising.

The lack of concern for, and understanding of, the reaction of the newborn to its bacterial environment is emphasized by the absence of any mention of the problem in two recent textbooks on pediatric dermatology. It has been said that the normal flora of the skin becomes fairly well established by the fourth day of life.[22] That this statement is not necessarily true has been demonstrated by studies of Hardyment,[19] Torrey and Reese[32] and Cunliffe.[10] All these studies are in essential agreement in that organisms can be cultured from the nasopharynx during the first few hours of life. With additional environmental exposure there is increasing incidence of positive cultures. Hardyment's observations on bacteriology and epidemiology of nursery infections are particularly apropos to our consideration of the staphylococcal problem. Starting with day one of the newborn period, nasal cultures were obtained from 1345 babies during each successive day of hospitalization. The carrier rate of babies increased each succeeding day for the period of hospital stay, ranging from 3 per cent nasal carrier rate on day one to 43 per cent by day ten. From this it is obvious that the duration of stay in the hospital increased the probability of the colonization of the infant's nose with *Staphylococcus aureus*. In comparing the rate of colonization of normal skin and that of the skin of infants with pyogenic infection it was shown that in the former group positive cultures were found in the groin in 19 per cent of 137 infants, 16 per cent in the anal area of 100 infants, and 20 per cent from the nose in 1345 infants. In a parallel study of the youngsters with pyogenic infections there was 79 per cent colonization from the anal area in 73 infants, 70 per cent positive cultures from the groin in 33 infants, and 81 per cent positive cultures from the nose. Although the studies were not designed to

record the establishment of the bacterial flora of skin, they do demonstrate that staphylococcal colonization of the nose and that of the normal skin run approximately parallel.

In a similar study in a newborn nursery, Shaffer[28] showed the striking correlation between the rate of bacterial invasion of the skin and the nasal carrier state in attendants in the nursery. All these studies also clearly demonstrate the role of strain type of organisms in the nasopharynx of attendants in establishing the resident flora of the skin of newborn infants in the nursery.

CHARACTERIZATION OF STAPHYLOCOCCUS AUREUS

The medical bacteriologist is not primarily concerned with classification or nomenclature, but is more concerned with the broad division and considerations which subdivide staphylococci into pathogens and nonpathogens, further subdivision being important only so far as it may shed light on the course of clinical infection. Although the morphology of the organism, its metabolic characteristics, antigenic structure and serologic classifications are of no interest to the clinician, various virulence factors (toxins) must of necessity be considered because of their relation to epidemiology and disease processes.[27, 35]

It has long been recognized that pathogenic staphylococci produce a full complement of toxins. These toxins are readily demonstrable in the test tube and are present in the pathogens and are lacking in nonpathogenic strains, but there is no direct evidence that they act similarly in vivo.[5, 9] It is not within the scope of this paper to discuss the virulence factors (hemolysins, lethal toxins, dermo-necro-toxins, leukocidin, enterotoxins, staphylokinase, hylauronidase and coagulase) which have been characterized and studied for staphylococcus, except to mention that detailed information about them may be found in the well documented paper by Shaffer et al. The exception to this broad general statement of course is the coagulase-producing capabilities of the organism; for it is generally agreed that this is the simplest and most practical laboratory measure of assessing the pathogenic potential of strains of staphylococci isolated from infections.

Unusual degenerative changes in staphylococci isolated from vaccine lymph were observed by Twort[33] in 1915. The effect was transmissible and was shown to be due to a group of viruses parasitic to bacteria. These bacteriophages[11] are of immense practical importance, for they serve as models of virus diseases which can be studied with relative ease. From our standpoint they are an invaluable epidemiologic tool for the precise type differentiation of strains, and serve as an aid in clarifying many of the unknowns involved in staphylococcal epidemics.

Although coagulase testing identifies the strain as pathogenic, prior

to phage typing no further classification was possible; for serologic classification failed to provide a discrimination fine enough to recognize strains isolated from separate sources or at different times as identical.[2] In this manner staphylococci obtained from the nasopharynx of a mother can be shown to be the same phage type as those organisms obtained from a furuncle on her daughter's skin.

Although phage typing is not a routine study which can be done in any microbiology laboratory, it is readily available in larger hospitals with a virology study section. Even in the smaller communities in some states it is available through the Department of Public Health, where the isolate from the local laboratory can be sent for typing.

The actual typing of an unknown staphylococcus with phage virus is quite easy. For routine typings, 19 basic bacteriophages have been recommended by the Subcommittee on Bacteriophage Typing of Staphylococci of an International Committee on Bacteriological Nomenclature[31] (Table 2).

TABLE 2. *Classification of Staphylococcal Bacteriophages*

GROUP I	GROUP II	GROUP III			GROUP IV	MISCELLANEOUS	
29	3A	6	54	(42B)*	42D	(31)*	(57)*
52	3B	7	70	(47B)*		(42C)*	(80)*
52A	3C	42E	73	(47C)*		(44)*	(81)*
79	55	47	75	(76)*		(44A)*	(142)*
(29A)*	(523)*	53	77	(VA4)*		(47A)*	

* Figures in parentheses are phage designations not included in the fundamental typing series used by most investigators.

The first step in typing of an unknown organism is accomplished by flooding an agar plate with a young culture of the unknown strain and removing the excess. After drying the surface of the plate, one drop of each of the commonly used phages is placed on the plate in a predetermined order, and the culture is placed in the incubator. Upon examination it will be found that on one or several of the areas treated with phage the surface growth of the staphylococcus has been completely or partly cleared. This is caused by the rupture of the growing cells by multiplication of the viral parasite. Staphylococci are seldom lysed by a single phage and are therefore referred to by their phage pattern, e.g. 40/42B, 80/81 (Fig. 12).

In recent years phage type 80/81 has received tremendous prominence, and it has been suggested that its frequency has been related to the indiscriminate use of antibiotics. A recent study by Blair and Carr[3] points out that type 80/81 was not an insignificant cause of staphylococcal disease long before its recent rise to notoriety. A study of the distribution of phage groups of *Staphylococcus aureus* in the years

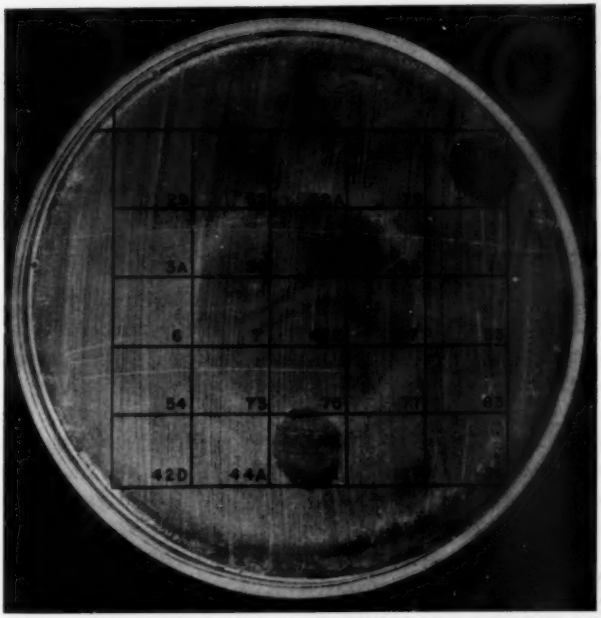

Fig. 12. Culture plate of coagulase-positive *Staphylococcus aureus* from a child with primary pyoderma, showing lysis of organism by phage types 80 and 81.

1927 through 1947, preserved as stock cultures, showed in the series of 176 strains that 94 were typable (53.4 per cent), and 82 (46.6 per cent) were nontypable. The number of typable strains showed phage patterns in several broad groups as follows: group I, 32.5 per cent; group II, 21.6 per cent; group III, 8.8 per cent; group IV, 4.6 per cent; type 80/81, 22.1 per cent. The occurrence of typable strains in the broad phage groupings corresponded closely to the frequency distribution of staphylococci reported in 1945 by Wilson and Atkinson.[36]

From these studies one can be certain that staphylococcus of the phage type 80/81, the so-called hospital strain, has been present for a long time. The antibiotic resistance of this strain is not completely clear, although it has been suggested that the resistance has been acquired as the result of contact of the organism with antibiotics. That the gene carrying resistance is biochemically different from that gene which determines phage selection of the host, and therefore typing, is illustrated in one instance by a penicillin-sensitive strain (52/52A/80) isolated from a case of osteomyelitis. This strain, after administration of penicillin, was inhibited by 50 units of the antibiotic, although the phage type was not changed. Of the original strains in this study which were studied for penicillin sensitivity, most were

sensitive to penicillin; therefore the suggestion that the resistance of 80/81 to antibiotics is a characteristic of acquired genetic alteration produced by antibiotics appears valid.

The versatility of these organisms is demonstrated by their extraordinary capacity to adapt to new and adverse environmental situations. The problem of antibiotic resistance is all too graphic proof of this capability.

EXPERIMENTAL INFECTION

Attempts at experimental production of infection on the cutaneous system of the human host have been undertaken in order to understand specific and nonspecific constitutional factors which maintain the cutaneous system in equilibrium with the bacteria-laden environment.

The earliest recorded attempt to test staphylococcal virulence in man was made by Garre[18] (1885), who produced multiple furuncles from which a large carbuncle developed by rubbing the skin of his forearm with a virulent culture of staphylococci. Pathogenicity of staphylococci was further established by Bumm[6] in 1885 and Bockhart[4] in 1887, who produced skin lesions by the injection of staphylococci subcutaneously; organisms from these lesions could be seen microscopically and grown on culture.

The early dramatic demonstration of staphylococcal virulence proved a limiting factor, and little experimental work has been performed in man since that time. The introduction of sulfonamides and the prevalence of superficial bacterial infections during World War II led Bigger et al.[1] and Sheehan et al.[29] to test the effectiveness of these chemotherapeutic agents under experimental circumstances. Although their studies were designed as an experiment in therapy, certain information about host-parasite relations can be gained from their experiences.

In attempts at the experimental production of impetigo, colonization was not easily established when the scarified skin of normal persons and that of patients with impetigo was inoculated with organism-containing fluid from patients with impetigo. In Bigger's study attempts met with complete failure, but Sheehan was able to produce a clinical infection indistinguishable from impetigo in 4 of 18 patients. The only difference in technique in the two experiments which seemed to contribute to the success in the latter was the covering of the area with an impervious cup after scarification and inoculation.

More recently Foster and Hutt,[17] under similar experimental circumstances using phage-typed strains 47/77, 52/80, and 3C/55/71, were regularly able to produce clinical evidence of infection when the traumatized inoculated areas were covered with a cover slip. Significantly,

there was no essential difference between the lesions produced by the different type of organisms, nor was there any difference in the results whether the inoculating dose was large or small. A similar observation about the size of inocula was made by Elek[12] in 1956 and Elek and Conen[14] in 1957 after intradermal injections of organisms obtained from healthy nasal carriers and from epidemic strains.

In all the early studies no attention was paid to the relation between the production of infection and the inoculum. In the Foster study, however, an attempt was made to quantitate the inoculum by dilution experiments. In these it was demonstrated that as few as 15 organisms could still produce significant sepsis in a standard skin lesion and that multiplication of organisms was so rapid that the total organism count at 24 hours was not much different from those infected with large inocula.[17]

In spite of the extensive reports which have accumulated on the epidemiology of staphylococcal infections, the factors which determine the development of septic lesions in any person remain largely unsolved. Although clinical evidence suggests that certain phage types of staphylococci are more virulent than others, experimental testing of this clinical observation by Foster, Elek, and Conen failed to demonstrate any difference in the smallest pus-forming dose and pathogenic phage type strains.

If these experimental pyogenic infections of the skin may be regarded as a template for host-parasite reactivity, it is difficult to avoid concluding that there is some unknown factor in the development of the infection. These facts tie in neatly with the clinical experience which suggests that pyogenic infection varies in contagiousness from the epidemics which are seen in newborn nurseries to the relative infrequency with which superficial bacterial infections are seen among adults, particularly physicians and nurses who are constantly and repeatedly exposed to pathogenic staphylococci.

It is an established clinical fact that despite the ubiquity of these organisms there are local and constitutional factors which contribute to the cutaneous system's resistance to infection. The well recognized clinical fact that infants, the aged, diabetics, and patients suffering from operative trauma are more susceptible to colonization and infection supports this statement.

CLINICAL STUDIES ON PHAGE TYPING IN BACTERIAL INFECTIONS OF THE SKIN

The question of whether certain phage types are more commonly associated with primary or secondary bacterial infections of the skin and

whether one type is more pathogenic than another in the production of skin lesions has been unanswered. The experimental production of lesions has suggested that there is no difference in the pathogenicity of various phage types.

Under the conditions of Foster's experimental production of bacterial infection of the skin with various phage types, he observed that one phage type was equally capable of producing disease as another. If this were the case, one would expect that the exposed cutaneous system would mirror in its clinical infections the phage types predominant in the environment. That this may not be so is suggested by Hardyment's observations[19] in the nasal cultures of normal mothers of newborns from 1952 to 1957 in which the incidence of V-81 infections was 1 in 100. If the nasal flora of these normal mothers can be considered an index of the availability of V-81 in the community environment, then we must assume that there is a difference in the pathogenicity of the different phage types so far as the skin is concerned.

In a study designed to test the applicability of the experimental observations on the importance of phage types in the production of clinical bacterial infections under "normal" circumstances, 158 cases of primary and secondary bacterial infections of the skin were studied in children and adults during an 18-month period (1959–60) (Table 3). Case selection was based on the presence of clinical evidence of infection and the presence of a positive smear and culture. All the isolates which were coagulase-positive were chosen for phage typing.

In the 158 cases studied it appeared that primary bacterial infection of the skin was more common in children than in adults, with 54 per cent (34 of 63) primary infections in children, and 37 per cent (35 of 95) in adults. On the other hand, secondary infection superimposed on a previously existing dermatitis was less common in children than in adults with an incidence of 46 per cent (29 of 63) in children as opposed to 63 per cent (60 in 95) in adults.

Of the children with primary infections, 23 per cent were due to type 80/81, and 35 per cent were nontypable; of secondary infections, 62 per cent were nontypable, and 3 per cent were type 80/81. In adults nontypable phage types were observed in 50 per cent of the primary infections, while 28 per cent of the infections were due to phage type 80/81; in secondary infections 38 per cent were nontypable, and 17 per cent were due to phage type 80/81.

These observations in primary bacterial infections show that phage type 80/81 is more pathogenic for the skin than other phage types. From these data it is clear that there is a difference in the pathogenicity of phage type in "natural" and experimental infection and that the prevalence of 80/81 is higher than in the general population.[7]

TABLE 3. *Bacteriophage Studies of Staphylococcal Infections in Children and Adults*

INFECTION	TOTALS	BACTERIOPHAGE					
		Nontypable	80/81	Group I	Group II	Group III	Miscellaneous (except 80/81)
Children							
Primary:	34 (54%)	12 (35%)	8 (23%)	3 (9%)	3 (9%)	6 (18%)	2 (6%)
Impetigo, folliculitis, furunculosis, ecthyma							
Secondary:	29 (46%)	18 (62%)	1 (3%)	1 (3%)	2 (7%)	4 (13%)	3 (10%)
Nummular eczema	8 (28%)	7 (87%)				1 (13%)	
Atopic dermatitis	7 (23%)	3 (43%)	1 (14%)		1 (14%)	2 (29%)	
Seborrheic dermatitis	6 (21%)	5 (83%)		1 (17%)			
Allergic contact dermatitis	4 (14%)	2 (50%)			1 (25%)		1 (25%)
Dermatophytosis	4 (14%)	1 (25%)				1 (25%)	2 (50%)
Adults							
Primary	35 (37%)	17 (50%)	10 (28%)	1 (3%)		2 (6%)	5 (14%)
Secondary	60 (63%)	23 (38%)	10 (17%)	3 (5%)	3 (5%)	10 (32%)	11 (18%)

DEGERMING CAPACITY OF THE NORMAL SKIN

We have suggested the presence of a delicate host-parasite relation in establishing a transient and resident flora of the skin. There has been much speculation about the role which the skin and its dermal appendages play in maintaining the cutaneous system in equilibrium with the pathogenic organisms in the environment.

The ubiquitous pyogenic staphylococcus in the nasopharynx and skin alike, with potential powers of pathogenicity, for the most part lives peacefully together with its human host. This relation between the staphylococcus, the skin and the nasopharynx is established at an early age[19] and is maintained throughout life. Opportunities must occur every day for disturbance of the equilibrium, yet the transformation from commensalism to parasitism is relatively infrequent.

To our knowledge there have been no studies on the cutaneous self-disinfection mechanisms in the infant. Invalid as our conclusions may be, all the knowledge of this capacity of the skin must be interpreted in light of experiments on adult skin. It would appear that the normal skin has enormous power for self-disinfection, although the actual mechanism of these protective capacities surely deserves more intensive study to explain adequately the clinical observation of the infrequency of staphylococcal infection. Burtenshaw[8] reviewed the subject and concluded that the following factors contribute to the ability of the skin to rid itself of bacteria: (1) desquamation and certain physical-chemical properties of the epidermis, (2) desiccation, (3) acidity of the skin, (4) the presence of fatty acids, (5) the action of ill-defined bacterial agents. These factors do not adequately explain the skin's capacity for self-sterilization.

The presence of inhibitory activity of micrococci on bacteria has been shown by Murray[24] and Evans.[15] The exact nature of this inhibition is not known, but the inhibition may be due to an antibiotic substance, incompatible pH, or other antagonistic activity.

The evidence indicating that damaged skin is less able to disinfect itself than normal skin is primarily clinical. It is important to point out that certain inflammatory eruptions of the skin, e.g. eczematous eruptions, are particularly prone to secondary bacterial invasion as opposed to other inflammatory diseases, e.g. psoriasis, which rarely if ever become secondarily infected.

Although there have been no attempts to produce experimental infection on the skin of the newborn, clinical observations strongly suggest that their skin is more prone to bacterial invasion than the thicker integument of older children and adults. The only definitive microbiological studies on the skin of the normal newborn and infant have been done in studies of epidemiology of newborn nursery infections. It

has been suggested that the vernix caseosa provides an antibacterial and protective barrier against bacterial invasion of the skin,[22, 30] but there is no experimental proof of this statement.

Clinical observations would suggest that those patients who are more prone to staphylococcal infections and those who have recurrent bacterial infections somehow fail to respond with protective antibody production. An immunologic deficit, therefore, might better explain the variation in susceptibility than local factors.

CLINICAL MANIFESTATIONS

As has been noted, the skin of infants and children differs from that of adults in its morphologic appearances, the type of resident flora, and in its resistance to bacterial infection. It is therefore not surprising to discover that it should react differently from the adult skin in its morphologic response to *Staphylococcus aureus*. It has been said that the morphology of the skin lesions (ready bullae formation) is due to the fact that the infant's skin is thinner and is less firmly attached to the underlying dermis. Because of immaturity of the cutaneous defenses there is a tendency to severe bacterial infections in the newborn infant (pemphigus neonatorum) (Fig. 13). That the ease of blister formation

Fig. 13. Pemphigus neonatorum in newborn, showing edema of face and exfoliation at site of flaccid bullae.

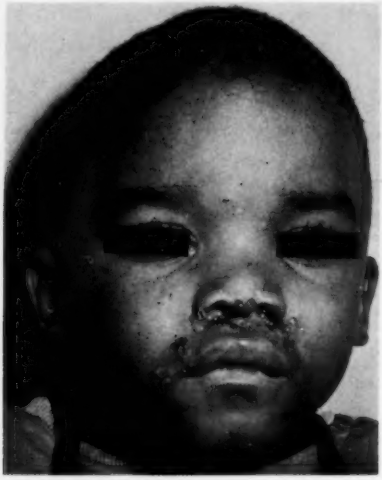

Fig. 14. Recurrent superficial pyoderma (impetigo) in a child with identical coagulase-positive *Staphylococcus aureus* on the skin and in the nasopharynx (phage type 80/81).

Fig. 15. Ecthyma showing crusted erosions following insect bites from which coagulase-positive *Staphylococcus aureus* was cultured.

could not be better explained on a biochemical basis rather than on an anatomic one has not been demonstrated.

Minor staphylococcal infections, which are by far more common than major ones, may be overlooked in the neonatal period because the only clinical evidence may be an insignificant pustular eruption which may be passed over as sweat retention syndrome or erythema toxicum neonatorum.

Some order is essential from the standpoint of classification, but it is not necessary to categorize the various morphologic disorders with complex descriptive dermatologic terms. It is sufficient to classify bacterial infections as primary acute superficial pyodermas and acute superficial infections appearing secondary to an existing dermatitic process.

Primary Acute Superficial Pyodermas

Primary pyodermas include such superficial infections as impetigo, ecthyma, follicular bacterial infections (furuncles), and eccrine sweat gland infections (periporitis).

Secondary Acute Superficial Pyodermas

Bacterial infection may appear as a complication of a wide variety of dermatitic processes, but in children and infants it is most frequently observed in atopic dermatitis, allergic contact dermatitis and seborrheic dermatitis.

As a final note in the discussion of the various clinical manifestations of pyogenic infections it is necessary to call attention to erythema streptogenes, a disease which in the most recent texts has been classified under the pyodermas (impetigo), but which has been repeatedly demonstrated to be a nonbacterial disease.[34] It would be far better to call this pityriasis alba, so that this entity is not confused with chronic bacterial infection.

Fig. 16. Secondary pyoderma superimposed on underlying atopic dermatitis.

Fig. 17. Pityriasis alba showing depigmented scaly patches with slight inflammatory changes at the periphery of the lesions.

MANAGEMENT OF STAPHYLOCOCCAL INFECTIONS

Although it is highly desirable to know how to treat a disease, it is far better to know what can be done to prevent it. It is, therefore, germane to our discussion to discuss prophylaxis, particularly as applied to prevention of bacterial colonization of the newborn's skin.

In studies in the newborn nursery it has been emphasized that the infant's nasopharyngeal and skin bacterial flora is established by contact with the attendants in the nursery and the mother. Shaffer[28] demonstrated that some of the nursery personnel were "permanent carriers" in that they harbored a strain of staphylococci in their nasopharynx which had a tendency to colonize others.[28] Most of the nursery personnel who became carriers, however, were "transient carriers." When the "permanent carrier" was removed from the nursery environment and while antibacterial measures were instituted, the strain disappeared from the nursery. Using the nasal and skin colonization rate as an index, it was shown that a hexachlorophene-containing soap substitute for bathing was superior to the conventional dry skin routine.

An understanding of the epidemiologic factors involved helps in the intelligent management of the newborn infant's skin. The nasal carrier state of the mother and of the nursery attendant has been emphasized.

Other factors which need to be considered in the bacterial colonization of the infant's skin are the nursery air, bedding, nurses' hands, and gowns.

In Hardyment's study[19] it was obvious that the carrier state was directly related to contact with the environment. Therefore major efforts should be made to control the staphylococcal environmental flora. This is best controlled by careful washing of the infant's handler's hands with pHisoderm containing hexachlorophene followed by cleansing with 70 per cent alcohol. The use of a neomycin-bacitracin preparation in the nostrils and beneath the nails of the mother and the attendants handling the infants is a useful adjunct. The gowns of the nursery personnel, babies' blankets and mothers' bedding are significant

Fig. 18. Seborrheic dermatitis with secondary pyoderma. *A*, Before treatment. *B*, Seventy-two hours after treatment with oral Chloromycetin alone, showing rapid response

sources of contamination. There appears to be no consistent relation between air contamination and the state of infection in the newborn nursery.

In addition to the local measures suggested for cleanliness, it would seem that there is good reason for segregation of long-stay infants and the establishment of "border" type nurseries because of the demonstrated rise in the rate of colonization in direct proportion to the period of stay in the newborn nursery.

The principal desire in the treatment of any bacterial infection is the elimination of the offending bacteria as quickly as possible. In skin infections the decision lies between a local or a systemic approach.

It is extremely important to appreciate what can be expected from appropriate antibacterial therapy in the way of host response to treatment. Assuming that the diagnosis is correct and that an appropriate antibacterial agent has been chosen for either local or systemic use, one should expect between 50 and 75 per cent improvement in the infection within 72 hours (Fig. 18). If this degree of improvement is lacking, the diagnosis should be questioned, or the possibility of an improper choice of antibacterial agent should be considered.

The question arises whether it is necessary to do smears, cultures and antibiotic susceptibility tests. We feel that it is a simple office procedure to do a gram stain on material from the suspected lesion. The presence of bacteria, and particularly gram-positive bacteria within polymorphonuclear leukocytes, supports the diagnosis of pyoderma. It is safe and rational to start treatment without culture and sensitivity studies on the basis of morphology of the skin disease and a positive smear for bacteria.

An antibiotic is chosen which has the best chance of being effective against the staphylococcus. According to our studies, a local preparation combining neomycin-bacitracin has a 95 per cent chance of being

TABLE 4. *Antibiotic Sensitivity Studies in Vitro on 180 Consecutive Cultures of Micrococcus Pyogenes from January, 1959, to January, 1960*

ANTIBIOTIC	SENSITIVE	RESISTANT
Erythromycin	75%	25%
Oleandomycin	81%	19%
Novobiocin	91%	9%
Chloromycetin	91%	9%
Tetracycline	53%	47%
Streptomycin	67%	33%
Bacitracin	90%	10%
Ristocetin	83%	17%
Penicillin	33%	67%
Viomycin	73%	27%
Neomycin	95%	5%
Vancomycin	86%	14%

effective. Of the antibiotics for systemic use, erythromycin is effective in 75 per cent of staphylococcal infections, oleandomycin in 81 per cent, and Chloromycetin in 91 per cent (Table 4). If the host response has not been satisfactory in 72 hours, cultures and susceptibility studies should be done and the appropriate antibiotic chosen on the basis of these studies.

General Considerations in Local Management

Local therapy is based on the premise that the antibacterial agent is brought in contact with the bacterium. It is absolutely essential to instruct the mother to cleanse the lesions gently and remove the crusts. Also, it is important to open pustules and incise and drain deep abscesses. We recommend pHisoHex rather than regular soap or soap containing hexachlorophene for cleansing both the infected and the normal skin. On the basis of our studies an ointment containing bacitracin and neomycin is the local agent of choice. If the infection is so widespread as to warrant systemic antibacterial agents, erythromycin is the antibiotic of choice. In most instances we feel that it is better to give local therapy for 72 hours, since the use of systemic antibiotics may produce resistant staphylococcal strains.

Chronic recurrent bacterial infections pose a real therapeutic problem. Under these circumstances it is wise to do an epidemiologic study of the family to determine whether there are nasal carriers (Fig. 19). It is advisable that all members of the family routinely use a soap substitute containing hexachlorophene followed by a 70 per cent alcohol wash. A neomycin-bacitracin ointment should be used in the nostrils and under the fingernails of all the members of the family. Intradermal administration of a stock staphylococcal toxoid is preferable to an autogenous vaccine.

CONCLUSION

It is difficult to escape the conclusion that there is some "x" factor in the development of pyogenic infections of the skin. This is emphasized by the variation in contagiousness of bacterial infection encountered in newborn nurseries in the past and the relative infrequency with which pyoderma is encountered among adults in general, as well as in physicians and nurses who are constantly and repeatedly exposed to pathogenic organisms.

The clinical observation that infants and children have an increased propensity for the development of pyogenic infections suggests that age may be a factor in susceptibility, although there have been no studies to demonstrate the reason for this.

Fig. 19. Infection with identical strain of *Staphylococcus aureus* (80/81) demonstrating infectivity with identical host response in a family group. *A*, Daughter. *B*, Son. *C*, Father.

Even though a substantial amount of work has been done on staphylococcal antibody production, correlation of infection with production of humoral antibodies and an understanding of the immune phenomena associated with staphylococcal infection is in need of more study.

In conclusion, we find that the skin of infants and children differs from that of adults in its response to bacterial infection. Little work has been done in determining normal bacterial flora of the skin of children.

but clinical studies of epidemics in newborn nurseries and of infections in older children emphasize the importance of the staphylococcus. In experimental infections no difference in ability of one phage type as opposed to another to produce infection could be shown, but clinical studies have shown clearly that phage type 80/81 is more pathogenic for the skin than other phage types.

Control of staphylococcal infections should be twofold: prophylactic measures in the newborn nursery and intelligent management of established skin infections.

In the treatment of infection a local preparation having a 95 per cent chance of effectiveness is one containing neomycin and bacitracin. A 72-hour trial of local therapy seems preferable to immediate use of systemic therapy with antibiotics because of the problem of development of resistant staphylococcal strains. If systemic therapy is necessary, erythromycin, 75 per cent effective, oleandomycin, 81 per cent effective, and Chloromycetin, 91 per cent effective, are the most likely to be effective.

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TINEA CAPITIS

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The hair falls off not altogether from the root, but piecemeal," so in 1736 Turner described a clinical entity which later proved to be caused by fungi.[27] The significance of this early description of tinea capitis was muddled by the lack of knowledge concerning etiology. Turner thought that the disease which he described was due to an infestation of the hair follicle. The importance of this original observation was not appreciated until Plumbe (1837) tried to bring some order to the chaos of morphologic description associated with diseases of the scalp. So that variations in morphology might not be confused as separate disease, he emphasized the necessity of appreciating the natural history of diseases.

An interesting historical note about the aura of mystery surrounding diseases of the scalp (porrigo) is Plumbe's verbalization of his frustration in the treatment of these problems. Aside from the confusion of different names for each morphologic variation and the inclusion of all other diseases of the scalp, the French at the venerable St. Louis Hospital had a secret treatment for the disease. The St. Louis Hospital at the time was the mecca of dermatologic knowledge where the great late nineteenth century dermatologists Alibert, Rayer and Biett worked. It was the diagnostic and treatment center of the day for all France, and in this great institution all the patients with diseases of the scalp (porrigo) were referred to the laymen Mahon and son for treatment. At that time the Mahons had treated 39,000 cases of diseases of the scalp by their secret method. In his text, "A Practical Treatise on the Diseases of the Skin," Plumbe asks the rhetorical question: How should these diseases of the scalp be treated? "I respond with great regret that we are not permitted to know it. M.

Alibert would have told us if he could; so would MM. Rayer and Biett. The secret rested twenty years ago with MM. Mahon, frere et fils, and now is confined to MM. les freres Mahon! Pity it is that the spirit of the three days of July did not visit the hospital of St. Louis!"[27]

After studying the natural history and various morphologic forms produced by infection of the scalp with dermatophytes, Plumbe states simply: "The forms I am about to describe each occasionally occur spontaneously but are also very frequently the results of infection. They have all the power of producing each other as I have ascertained beyond doubt in a variety of instances: a fact which is perhaps by itself sufficient to establish their identity."[27]

Sabouraud's studies on ringworm of the scalp at the turn of the twentieth century were the major contribution to the knowledge of the organisms causing infection of the scalp and the host-parasite relation. It is the purpose of this paper to review new information about the host-parasite relation as shown by experimental infection on the human scalp, and the treatment of the infection with an antibiotic.

Tinea capitis is produced only by the Microsporum and Trichophyton species of the dermatophytes. The Microsporum species concerned in tinea capitis are *M. audouini*, *M. canis* (felineum), *M. gypseum*; and Trichophyton species: *T. ferrugineum*, *T. Schoenleinii*, *T. violaceum*, *T. verrucosum*, *T. tonsurans*, *T. mentagrophytes*, *T. rubrum* (rarely). Although these organisms may produce clinical infections which are indistinguishable, *T. violaceum* (blackdot disease) and *T. Schoenleinii* (favus) each produce a specific clinical picture.

Various species may be seen in different geographic areas, but from the standpoint of our discussion we need not distinguish between the species, for they all respond equally well to griseofulvin.

EXPERIMENTAL INFECTION

It is essential to understand the natural history of the disease, and for this purpose we shall use *M. audouini* as the model of dermatitic infection. The understanding of the course of *Microsporum audouini* infections is based on Sabouraud's original observations and Kligman's study of experimental infections on the scalp of human beings.[17, 33] The observations were made on experimentally inoculated areas on the scalps of human volunteers at regular intervals after inoculation and infection. Precise information was obtained which is applicable to clinical infection on the scalp caused by either the Microsporum or Trichophyton species.

After a brief incubation period of four to five days, the spores which have been placed in the stratum corneum or in the hair follicles germinate and produce a mass of fungal elements in the orifices of the

hair follicles. The initial growth is around the hair and into the orifice of the follicle on the hair surface. Fluorescence of the hairs is not present at this time, but appears within one week of inoculation at the time when there is invasion of the hair shaft. The first invasion of the hair shaft occurs at a midpoint in the intrafollicular portion of the hair. During this period of invasion there is also proliferation on the surface of the stratum corneum with extension of the infection radially away from the point of inoculation. As additional pilosebaceous orifices are involved in the spreading process, invasion of more and more hair follicles occurs. Within two weeks the organisms have extended down the hair follicle to their deepest point of invasion (keratogenous zone). Concomitant with this complete invasion of the hair follicle, the fungi within the hairs begin to alter the keratin and the hairs begin to break off. This entire process may require approximately three weeks to develop, and during this period there is little evidence of clinical infection.

In biopsy specimens of the experimental infection the fungal elements within the hair follicle rapidly reach a lower level which corresponds to the upper limit of the keratogenous zone of the hair matrix, a point which is about 0.5 mm. above the papillae. At this point (Adamson's fringe), although the cells are almost completely keratinized, they still retain their nuclei. It is striking that invasion by the organisms never goes beyond this point. The absence of further invasion has been said to be due to the necrophilic properties of the organism and its inability to proliferate in nonviable or semiviable tissue. The same phenomenon is observed on the skin, where the organisms have been demonstrated to invade only the keratinous area of the epiderm. The work of Lorincz[19] and Blank[4] with the antidermatophytic serum factor has demonstrated conclusively that the inability of the fungus to invade further is not due to its "keratinophilic growth requirement."

HOST-PARASITE RELATION

The first suggestion that there were host factors in limiting dermatophytic invasion of the skin was shown by Ayres, Sr.,[1] in 1934 and, later, Peck[26] in 1940. They demonstrated the inhibitory effect of blood serum on dermatophytes grown on Sabouraud's medium. In a laboratory refinement of these observations, Lorincz demonstrated the presence of a globulin fraction in the serum which had potent antidermatophytic activity and is capable of limiting dermatophytic growth to those layers of the skin outside the epidermal water-barrier zone. Using the organ culture technique, Blank graphically demonstrated the fallacy of the keratinophilic growth requirement. By this technique

he showed the absence of invasion by organisms if the culture medium contained human serum and the presence of invasion into the dermis when the serum factor was absent from the culture medium. The report of a case of pulmonary invasion by *Trichophyton mentagrophytes*[12] indicates that this factor may be absent on rare occasions.

In a study designed to explain the increased frequency of tinea capitis in prepuberal children Rothman[32] demonstrated fungistatic activity of long-chain, odd-numbered fatty acids which are secreted by postpuberal sebaceous glands in increased amounts as compared to the sebum of children.

CLINICAL PICTURE

The striking change seen in tinea capitis is alopecia with broken-off hairs. The infected areas are circumscribed and often become confluent to form gyrate patterns. Early in the disease it is not uncommon to find a single patch; more commonly, multiple areas of infection are found. The areas of infection may vary from a few centimeters in diameter to almost complete involvement of the scalp (Fig. 20). During the first six to eight weeks of infection, while the patch is still enlarging, there may be a slightly elevated inflammatory border, while the remainder of the lesion is dry and scaly. During the early stage of invasion, mycelia may be found in scales from the scalp, but later the organisms may be absent in the scale and may be found mainly around and in the epilated hair. Generally the infection is asymptomatic, although a secondary inflammatory (kerion) reaction may occur (Fig. 21).

The Wood's light, which emits essentially monochromatic ultra-

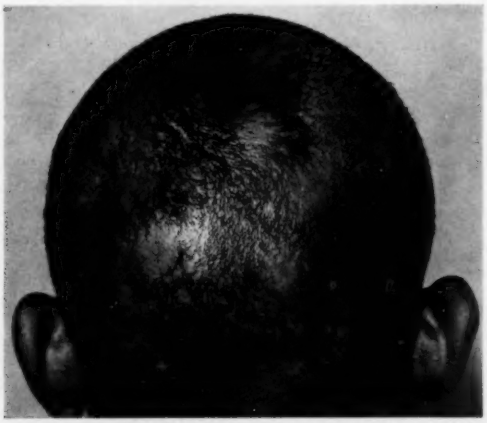

Fig. 20. Tinea capitis caused by *M. audouini* in a 7-year-old boy, showing circinate and confluent patches of alopecia with broken-off hairs.

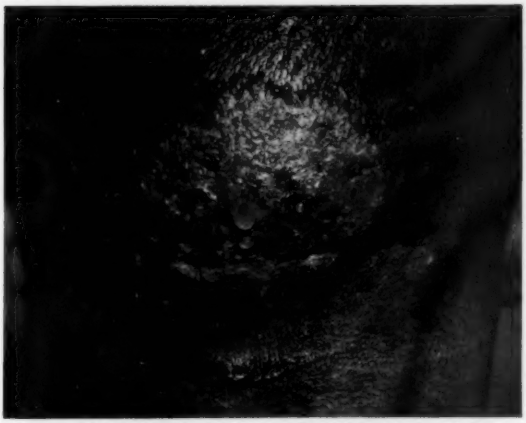

Fig. 21. Kerion caused by *M. audouini* in an 8-year-old boy, showing a raised, edematous, boggy area with serum discharge and right occipital lymphadenopathy.

violet irradiation in the range of 3650 Angstrom units, is invaluable for the detection of infection and determining the extent of involvement. Only *Microsporum audouini* and *canis*, however, of all the organisms which produce ringworm of the scalp, show the typical greenish-white fluorescence. *T. gypseum*-infected hairs show bluish fluorescence. The material which is responsible for fluorescence is a product of the growth of fungus within the hair and may be extracted in boiling water. The possibility of false-positive or false-negative fluorescence of hairs should be considered if local preparations have been applied to the scalp before examination. Tar-containing preparations and compounds containing a petroleum most often produce confusing fluorescence.

Microscopic examination of the infected hairs in a potassium hydroxide preparation is necessary for positive diagnosis; culture is necessary for species identification. The spores will be seen predominantly around the hair-ectothrix (*M. audouini, M. canis, M. gypseum; T. mentagrophytes, T. rubrum* and *T. ferrugineum*) or predominantly within the hair-endothrix (*T. tonsurans, T. violaceum, T. Schoenleinii*). In many instances the morphology of the culture may be sufficiently characteristic to make a diagnosis, but it is usually necessary to study microscopic preparations of culture mounts or to do other special procedures to make a conclusive species differentiation.

DIFFERENTIAL DIAGNOSIS

Alopecia areata, trichotillomania, monilethrix, and hair loss due to inflammation (seborrhea and pyoderma) must be considered in differential diagnosis of diseases of the scalp.

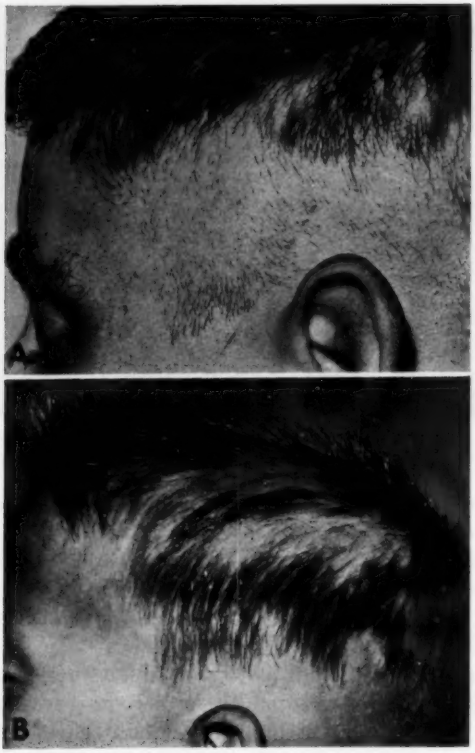

Fig. 22. A, Alopecia areata in 13-year-old boy, showing area of alopecia with broken-off hairs. B, Alopecia areata in 7-year-old boy with scattered areas of alopecia.

In *alopecia areata* there is a sudden, patchy loss of hair. Early in the disease there may be an inflammatory reaction on the skin and scattered broken-off hairs, while later there is complete hair loss (Fig. 22). The absence of scaling and nonfluorescence under the Wood's lamp make the differential diagnosis easy.

In *trichotillomania* irregular areas of broken-off hairs are present. The stubble are not easily epilated, nor do they break off (Fig. 23). Scaling of the skin in the involved patches is not observed, and there is no fluorescence under the Wood's lamp.

In *monilethrix*, patchy areas of broken-off hairs in the occipital region and neck are seen (Fig. 24). The disease is frequently associated with follicular keratotic papules, the hairs break easily on manipulation, and alternate constrictions of the hair shaft can be seen under the microscope.

Postinflammatory hair loss which can closely simulate tinea capitis

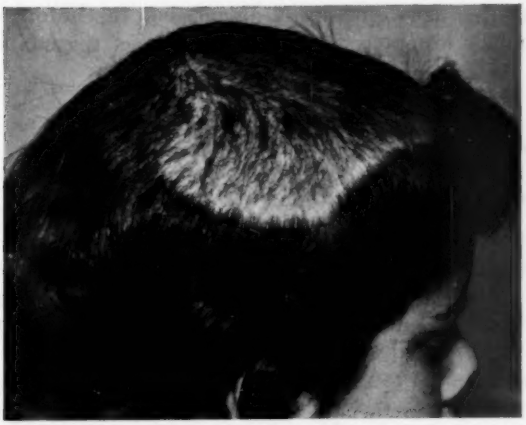

Fig. 23. Trichotillomania in 14-year-old girl, showing broken-off stubble on vertex of scalp.

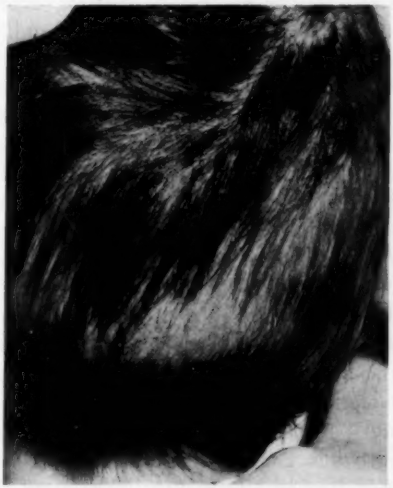

Fig. 24. Monilethrix showing areas of alopecia with broken-off hairs and macroscopic beading of the hairs.

is seen in some cases of seborrhea. In these cases the hairs may be easily epilated and there is a scaling patch at the site of involvement. The Wood's lamp examination does not show fluorescence, and the potassium hydroxide preparation is negative.

Sensitization of the host to the invading organism produces an inflammatory lesion with crusting, serosanguineous discharge, and postcervical lymphadenopathy which simulates pyogenic infection. At this

stage fluorescent hairs are usually absent, but the history of a scaly patch with hair loss preceding the inflammation suggests the proper diagnosis.

TREATMENT

Griseofulvin

Faced with the public health aspect of ringworm infection of the scalp, physicians responsible for its treatment in children had, of necessity, to use the therapeutic modality most likely to produce a cure. In the absence of a uniformly successful local fungistatic or fungicidal agent, epilating doses of x-ray were the therapy of choice. The intrinsic dangers of ionizing irradiation have forced a reconsideration of this means of therapy.

The recent discovery of the clinical usefulness of griseofulvin in dermatophytic infections was stimulated by its use as an agricultural antifungal agent and by the success in treating experimental *Microsporum gypseum* infection in guinea pigs.[13] The studies demonstrating the influence of serum factors in superficial fungus infections illustrated the possible importance of blood-borne substances in treating cutaneous and hair follicle infections by dermatophytes.[4, 19]

The events leading up to the treatment of dermatophytic infections with a specific oral agent commenced in 1939 when Oxford[23] isolated a metabolic product of Penicillium. In 1946 Brian and his colleagues[9] extracted from culture medium of *Penicillium janczewskii* a curling factor which was so named because it caused stunting and distortion of the germ tubes of *Botrytis allii*, a cause of infection in lettuce. In 1947 Grove and McGowan[16] showed that the curling factor and griseofulvin were clinically identical, and Brian obtained biological confirmation of the identity. Brian and Napier[7, 8, 22] originally studied griseofulvin as an agricultural antifungal agent, but the effect of the agent against fungi pathogenic for man and animals was completely ignored until 1958, when Gentles reported the successful use of orally administered griseofulvin in guinea pigs experimentally infected with *Microsporum canis* or *Trichophyton mentagrophytes*. Shortly thereafter Lauder and O'Sullivan[18] showed the effectiveness of this antibiotic in calves previously infected with *Trichophyton verrucosum*.

The first clinical paper on the use of oral griseofulvin in man was read by Riehl[28] in November, 1958. In December, Williams et al.[36] published a preliminary report, and a leading article in *Lancet* summarized the recorded work and urged further investigation.

The investigation in this country was initiated by Blank[3] shortly after the appearance of Gentles's paper. He treated a patient with a

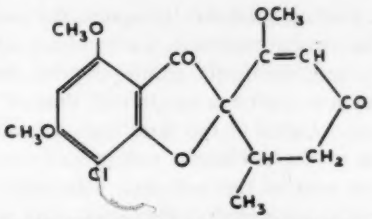

Fig. 25. Chemical structure of griseofulvin.

severe generalized cutaneous *Trichophyton purpureum* (*rubrum*) infection with griseofulvin and observed a prompt response. Since the original observation, and after the early investigative studies in this country which culminated in an International Symposium on Griseofulvin,[15] many articles have been written about the effectiveness of griseofulvin in dermatophytic infections.

CHEMISTRY. Griseofulvin is a white powder which is slightly soluble in water and has fungistatic and colchicine-like activity. It is a fermentation product of Penicillium (*P. patulum, P. griseofulvin* and *P. janczewskii*). The antibiotic was first isolated by Oxford and is a thermal-stable compound which chemically is 7-chloro, 2-4,6, trimethoxy-6 methylspiro [benzofuran 2 (3H), 1-(2) cyclohexene] (-3,4-dione) (Fig. 25).

At a pH of 7 it is slightly soluble in water (0.001 per cent), methanol (0.1 per cent) and ethanol (0.1 per cent), and quite soluble in N-N dimethylformamide (12 per cent). In solution the drug withstands autoclaving at 250° F. for 30 minutes at a pH of 7, without loss of potency. It is stable in the dry form for at least 20 months at 100° F.

ABSORPTION, DISTRIBUTION AND EXCRETION. The studies of Bedford's group[2] on the biological distribution of griseofulvin in experimental animals provided pertinent information about absorption, distribution and fate of the drug. They showed that griseofulvin appears to be evenly distributed throughout the tissues; measurable concentrations occur in the lungs and the skin after intravenous injection, and in the liver, skin, skeletal muscle and fat after oral ingestion. After a single intravenous dose, 90 per cent of the drug disappeared in the first 5 minutes, followed by decreased rate of loss, until little of the drug remained after 4 to 6 hours. But less than 0.4 per cent of "free griseofulvin" appeared in the urine after intravenous injection. It would seem, therefore, that the rapid disappearance of griseofulvin from the blood was due to rapid dissemination into the tissues. Sharpe and Tomich[34] found that intraperitoneal administration in rats was 90 times more toxic than the oral dose. This finding suggested that in high doses, at least, griseofulvin is either poorly absorbed from the gastrointestinal tract, or well absorbed, and then rapidly destroyed.

In spite of the limited solubility in water, the antibiotic is quickly absorbed from the gastrointestinal tract. Using spectrophotofluorometric assay techniques, Bedford's group[2] showed that the peak blood level occurred four hours after a single oral dose of griseofulvin. The compound was concentrated in the skin, liver, fat, and skeletal muscle. About 50 per cent of the antibiotic is destroyed within 6 hours of ingestion. Sixteen per cent of the oral dose is excreted in the feces, and less than 1 per cent is recovered in the urine after administration. Experiments with rat tissue splices showed that griseofulvin was rapidly destroyed by the liver at the rate of 1.1 micrograms per gram of wet tissue per minute, but was not inactivated by the spleen, lung or kidney. It is absorbed from the duodenum, jejunum and ileum and to a small extent from the stomach and even less from the rectum, but there is no absorption from the colon. Of the griseofulvin circulating in the blood, 65 per cent is in the plasma, and of this, 84 per cent is protein-bound; thus 55 per cent of the total amount is bound with protein.

Gentles and his co-workers[14] reported the presence of active griseofulvin in the hair of guinea pigs. In animals given 60 mg. per kilogram of body weight for 3 weeks, 6 micrograms of the antibiotic per gram of hair was found in the hair. Since half of the griseofulvin was extracted from the hair by cold water and the remainder by hot methanol, these workers concluded that the antibiotic is not chemically bound to the keratin, but occurs mainly as a simple deposit. The transport of the antibiotic depot outward by subsequent hair growth blocks further invasion of the fungus, and the parasite is eventually eliminated by removal or loss of the infected portion of the hair.

Roth and Blank[30] demonstrated the presence of griseofulvin in human stratum corneum and determined its rate of transport through the epidermis. Transport of griseofulvin to the hair follicle and deposit in the hair are probably accomplished in the same way. In their study a direct bioassay procedure was done in vivo in which the macroconidia of *Microsporum gypseum* were applied to the skin of the inner surface of the forearm in microslide ring cultures. The presence of the antibiotic in the stratum corneum was established by the induction of morphologic abnormalities in the emerging germ tubes of the spores. Although germination of the macroconidia was not inhibited, clubbing, distortion and branching of the primary hyphal elements were observed.

The progress of griseofulvin through the thickness of the stratum corneum was determined by stripping off the cornified cellular elements to the desired depth with multiple applications of Scotch tape. By this method the antibiotic was detected at the junction of the stratum corneum and stratum mucosum in 48 to 72 hours after the

onset of therapy. The time required for the transport of the antibiotic to most superficial portions of the epidermis was directly related to the thickness of the horny layer of the patient's skin.

Mechanism of Action. When griseofulvin is given to rats intravenously (100 to 200 mg. per kilogram of body weight), mitotic arrest in the metaphase is produced in actively dividing cells.[24, 25] In this respect griseofulvin is similar to colchicine in that it likewise induces arrest of dividing cells in metaphase. Colchicine does not inhibit the growth of dermatophytes, however, nor does griseofulvin produce a severe toxic manifestation in rats that may be observed with colchicine at levels which produce the same extent of inhibition of mitosis. Although the net results of griseofulvin and colchicine on mitosis are the same, there is no evidence that this is achieved by the same mechanism.

In biochemical studies on the metabolism of griseofulvin, McNall[21] suggests that griseofulvin may act as a competitive analog at one or more steps in the biosynthesis of nucleic acid, since the purine ribocides and griseofulvin are structurally similar. If the interference of nucleic acid synthesis is due to inhibition at the polymerization state during the replication of chromosomes, it indeed would be expected that inhibition would occur as it does at metaphase. He further suggested that the variety of morphologic changes produced by griseofulvin when growth is partially inhibited was due to antibiotic interference with cell wall synthesis.

The implication is that the griseofulvin acts on the growing mycelia by deluding the cells into taking up the antibiotic in place of the normal nucleic acid precursor and thus disorganizes the metabolism of the dermatophyte much as folic acid antagonists act on the dividing cells in a lymphomatous process.

Blank's studies[6] on the effect of griseofulvin on dermatophytes under the electron microscope suggested that though the major effect on the dermatophyte is fungistatic, the youngest actively metabolizing fungal cells are killed by griseofulvin, but the older, more dormant elements are not so drastically affected. A comparison of the mycelia before and after exposure to griseofulvin showed swelling and ballooning of the mycelial elements. The cell wall loses integrity and splits appear, although the wall may become thickened. The cytoplasm almost disappears, leaving a few shriveled remnants of the cytoplasmic membrane filled with spherical, osmophilic lipid bodies (Fig. 26).

A histopathologic study by Burgoon and Graham[10] on the effects of griseofulvin in *M. audouini* infections of the scalp in children demonstrated the effect of the drug on hair follicle invasion, the response of the infection to varying dose schedules, and finally the lack of colchicine-like effect on the matrix of the hair.

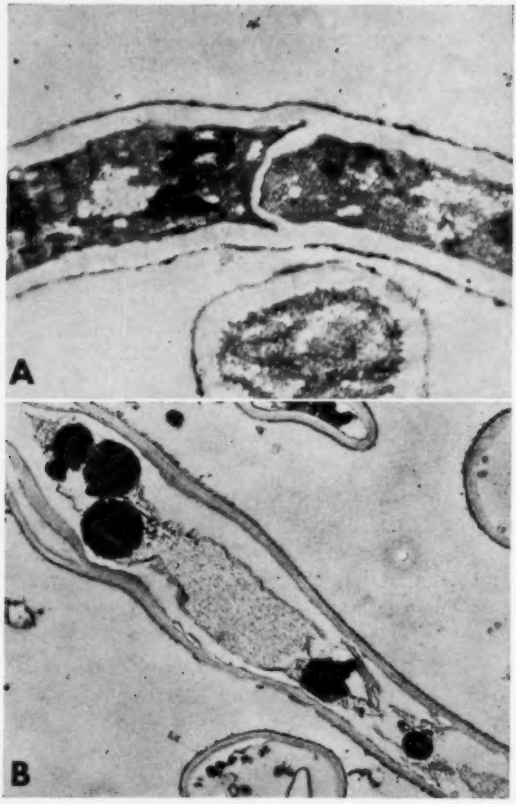

Fig. 26. A, Electromicroscopic view of *Trichophyton purpureum* mycelia, showing normal structures with thick cell wall. × 22,500. (Courtesy of David Taplin and Harvey Blank, Department of Dermatology, University of Miami Medical School.) *B*, Electromicroscopic view of *Trichophyton purpureum* mycelia after treatment with griseofulvin, showing distortion of cell wall with splits and shriveled remnants of the cytoplasmic membrane filled with large osmophilic lipid bodies.

Biopsy specimens of infected areas of the scalp in 20 children were studied histopathologically in serial sections cut parallel to the surface of the skin. In these parallel serial sections several objective landmarks could be used as guideposts for determining the level of the infection in the hair follicle. These anatomic landmarks are the hair bulb, matrix, and papilla, the keratogenous zone, the arrectores pilorum muscle, the sebaceous gland bulge, the stratum malpighii and the stratum corneum (Fig. 27).

The infected hairs were observed in serial sections from the depths of the skin at the level of the hair bulb to the surface at the level of

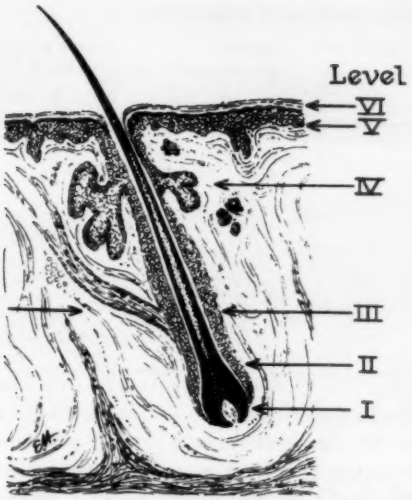

Fig. 27. Diagram of pilosebaceous follicle showing the objective landmarks. Level I, hair bulb (matrix and papilla); level II, keratogenous zone (*KZ*); level III, arrectores pilorum muscle (*APM*); level IV, sebaceous gland bulge (*SG*); level V, stratum malpighii (*SM*); level VI, stratum corneum (*SC*).

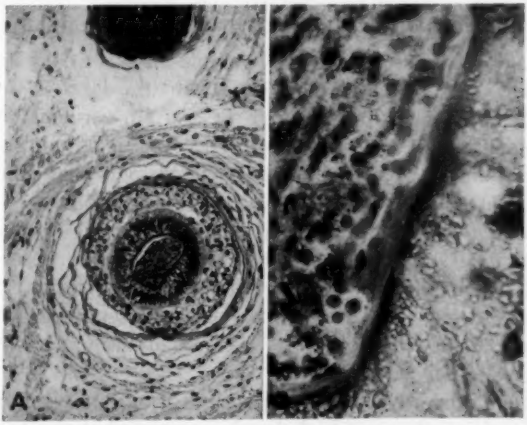

Fig. 28. Level II. A few microspores are present in the area of the cuticle of the cortex and inner root sheath. Some spores appear to be invading the cortex. Note melanin pigment granules adjacent to spores. Trichohyalin granules are prominent in Huxley's layer. × 130, × 1,200.

the stratum corneum. It was possible to follow each hair and determine the level of infection at predetermined intervals after oral administration of griseofulvin. In untreated controls, spores were observed lying free in the hair follicle down to the level of the keratogenous

TABLE 5. *Time-Dose Response to Griseofulvin*

GRISEOFULVIN DOSAGE	BIOPSY DAY	LOWEST LEVEL AT WHICH SPORES WERE OBSERVED				
		KZ	APM	SG	SM	SC
Control		+	+	+	+	+
Single dose:						
4 gm.	14	−	+	+	+	+
5 gm.	11	−	+	+	+	+
4 gm./day for 7 days	11	−	+	+	+	+
0.5 gm./day	7	−	−	+	+	+
	14	−	−	+	+	+
	21	−	−	−	+	+
	28	−	−	−	+	+
	35	−	−	−	−	+

zone (Fig. 28). In the untreated cases spores were not limited to the upper portion of the keratogenous zone, but were seen along its length. In no instance were spores observed at this low level of the follicle after one week of treatment. Table 5 shows the relations between dosage of the drug, time elapsed after administration of various dosage schedules, and the site of spores along the hair follicles. There was no relation between location of the spores in hair follicle and the amount of drug administered by single or multiple dose schedule.

Spores subsequently disappeared in a continuous stepwise pattern from the level of the arrectores pilorum muscle at 14 days to the level of the sebaceous gland bulge by 21 days, and the level of the stratum malpighii by 28 days, and the level of the stratum corneum by 35 days. The extermination of the spore mycelial level in a hair follicle was approximately linear with time, when one considers that hair grows at the approximate rate of 0.35 mm. per 24-hour period.

The hair root of the human scalp is a tissue of high metabolic and mitotic activity. One would expect, therefore, that griseofulvin with its proved colchicine-like potentialities would produce metaphase arrest of the matrix cells if sufficiently large doses were given. With doses up to 140 mg. per pound of body weight no obvious metaphase arrest was observed.

This study indirectly confirms Gentles's work in experimental infections in guinea pigs in which he demonstrated that griseofulvin is incorporated in the keratin of the hair. The histopathologic observations in the human follicle infection showed that there was no further downward extension of the infection along the hair shaft after griseofulvin had been started. A graphic demonstration of the abrupt line of demarcation at the point in the hair shaft at the time griseofulvin was started can be shown by periodic acid Schiff staining of hairs (Fig. 29).

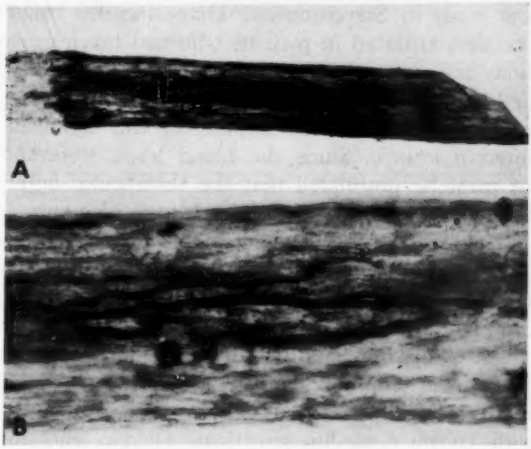

Fig. 29. A, Treated tinea capitis, 0.5 gm. per day for 3 weeks (reduced 20 per cent from original magnification). Whole mounts of hair are periodic-acid-Schiff-reactive. Whole mount of hair in which clinical demonstration revealed fluorescence only at the distal end. PAS-reactive mycelia are present, changes limited to the tip. × 8, × 145. B, Mycelial forms only. × 440.

SPECTRUM OF ACTIVITY. The spectrum of activity of griseofulvin is all-inclusive so far as the dermatophytes producing ringworm infection are concerned. Although the different dermatophytes have different levels of sensitivity, they are all responsive to the blood levels which can be obtained by oral medication with the drug.

MINIMUM INHIBITORY CONCENTRATION OF GRISEOFULVIN FOR DERMATOPHYTES: MICROGRAMS/ML. IN VITRO[31]

M. audouini	0.40–0.46
M. canis	0.20–0.24
M. gypseum	0.42–0.46
T. mentagrophytes	0.38–0.42
T. rubrum	0.14–0.18
T. tonsurans	0.28–0.32
T. violaceum	0.36–0.40
T. Schoenleinii	0.34–0.38

Strain resistance of the dermatophytes to griseofulvin has been looked for by most investigators, and Robinson[29] has demonstrated acquisition of resistance in vitro. In this study the fungi were transferred successively in solid media containing increasing concentrations of the antibiotic to a maximum of 30 micrograms per milliliter. The strains of *T. mentagrophytes*, *M. canis* and *M. audouini* developed strong resistance to the drug. The mechanism of resistance appeared to be due to the production of enzymes by the fungi which reduced griseofulvin to a biologically less active compound.

In a recent study by Stevenson and Djavahiszwili[35] strain resistance could not be demonstrated in patients who had taken griseofulvin for nail infections for as long as one year. In several patients whose infection failed to respond to the recommended dosage of the antibiotic, pretreatment and post-treatment isolates of the organism failed to show acquired resistance. Since the blood levels were shown to be adequate, it must be postulated that the therapeutic failure was due to absence of the drug in the keratinized tissue elements.

Side Effects. In spite of the widespread administration of griseofulvin, it has been shown to be a drug of remarkably low toxicity, there being no reports of significant toxic manifestations. Occasionally, patients complain of headache or mild gastrointestinal disturbances such as nausea or diarrhea. Various drug eruptions with vesicles, urticaria, maculopapular eruptions have occasionally been described. Cross sensitivity with penicillin has not been recorded, and indeed, even in patients with known penicillin sensitivity, allergic reactions have not been recorded. No abnormalities of liver or kidney function or blood chemistry have been observed. The marrow and peripheral blood cell counts have shown no deviations that could be attributed to griseofulvin.[3, 5]

As a result of the studies by Paget and Walpole[24] demonstrating mitotic arrest of actively dividing cells in the testicles of experimental animals with intravenous intraperitoneal administration, extensive studies have been carried out by MacLeod[20] in human beings. With oral dosage there were no apparent effects of griseofulvin on spermatogenesis. In addition to studies on sperm counts, motility and morphology, testicular biopsies were taken from patients after 12 weeks of treatment; no histologic abnormalities were observed.

Dosage. Numerous preliminary reports suggest the usefulness of griseofulvin in the treatment of tinea capitis. A study in prepuberal children was designed to determine the most effective treatment schedule.[11] The study, which began in February, 1959, reports final follow-up 6 months to one year after treatment in 91 children, of whom 9 were girls. Seventy-four children had infections due to *Microsporum audouini*, one due to *Trichophyton rubrum*, and in 16 instances there was no growth on culture. In all the patients the diagnosis was established by typical fluorescence under the Wood's light, and demonstration of spores by direct preparations. During the period of the study no local therapy was used on the scalp, nor was any special routine for scalp care suggested.

The results of treatment may be seen in Table 6, in which the dosage is expressed in milligrams per pound of body weight. The only group with a large number of failures was that in which single doses from 9 to 32 mg. per pound were given. Of the 24 children in this

TABLE 6. *Results of Therapy with Griseofulvin*

DOSAGE SCHEDULES	CURES	FAILURES
Single doses:		
9.1–17 mg./lb.	5	11
27.9–32.4 mg./lb.	2	6
60.0–114.1 mg./lb.	10	4
Multiple doses:		
1 week of therapy:		
9.8–40 mg./lb., alternate days	11	1
55–64 mg./lb. daily	1	3
2 weeks of therapy:		
8.9–12.1 mg./lb. daily	11	0
3–7 weeks of therapy:		
10 mg./lb., alternate days or less	6	1
10 mg./lb. daily or less	17	2
15 mg./lb. daily or less	1	0

group, 17 were treatment failures. The single dose schedules of 60 mg. per pound resulted in 10 cures out of 14 patients. The multiple dose routine produced a high cure rate in all the groups, although it should be noted that treatment for one week was as effective as treatment for seven weeks.

Cure was usually evident in three to six weeks, at which time nonfluorescent hair could be seen emerging from the hair follicle while the tips remained fluorescent (Fig. 30). In 3 cases, 10 or fewer bright fluorescent hairs which were positive by direct examination remained after complete regrowth of all infected hairs. The importance of direct microscopic examination of persistently fluorescent hairs must be emphasized, for occasionally fluorescence will remain in the absence of any mycelia.

There were no signs of serious toxicity, and the only minor untoward effects were mild diarrhea, headache or nausea.

On the basis of this study and others, a dose of 10 mg. per pound of body weight for one week should be sufficient to cure most cases. Under certain circumstances it may be more advantageous to give a single large dose, although in our experience this alters the effectiveness (approximately 75 per cent cure rate). Although various manipulative measures on the scalp may be used as part of the treatment, they are not necessary for a cure.

CONCLUSION

Treatment of tinea capitis, once a problem to the clinician, has now been revolutionized, owing to the discovery of the effectiveness of the oral administration of the antibiotic griseofulvin. A dosage of 10 mg.

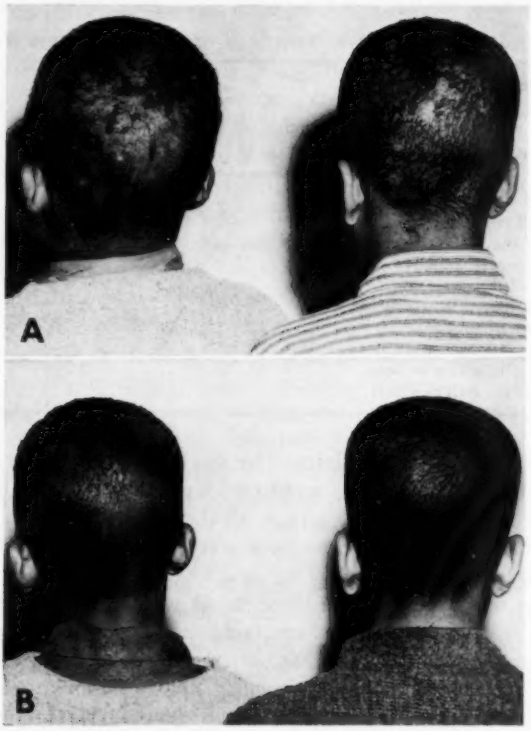

Fig. 30. *A*, Tinea capitis due to *Microsporum audouini* in siblings prior to treatment with griseofulvin. *B*, No evidence of infection after 8 weeks' treatment with griseofulvin.

per pound of body weight per day for one week will produce a cure in almost 100 per cent of cases. In certain situations in which a single large dose is the only means of assuring treatment, 60 mg. per pound produces a cure in approximately 75 per cent of cases, and may be given without fear of any serious toxic reactions. Cure becomes evident in three to six weeks.

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ACNE VULGARIS

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Even before the first teen-age cave girl was abducted as she sat in front of the family grotto sunning herself to improve her acne, the problems of this disease had beset mankind. Though the condition was referred to by the Greeks as *ionthoi* and by the Romans as *varus*, the first recorded use of the word "acne" occurs, according to MacKenna,[20] in the *De Re Medica* of Aetius in A.D. 542. There is no certainty as to the precise derivation of the word "acne," two suggestions being that it arose from the Greek *akne*, a peak, or from *a-knao*, without itch.[20] Acne vulgaris, as an entity, was introduced into medical nomenclature by Fuchs[10] in his textbook in 1840 when blackheads were thought to be worms with their heads buried in the skin sucking nutritious material from their host: hence *comedo* (Latin—a glutton), also introduced by Fuchs.

It has been variously estimated that between 80 and 95 per cent of juveniles and adolescents exhibit some manifestation of acne, so that its presence, however mild, may be regarded as one of the hallmarks of this stormy period of life. This fact, however, does not make acne any less of a problem to the patient, nor does it absolve the physician from therapeutic responsibility. Such platitudes as "You'll grow out of it" or "It's part of growing up" are little consolation to the teenager who feels that his acne is ugly and repulsive. Judicious use of topical and systemic therapy in friendly hands can do much for the patient's social comfort. Take care that when you say, "Nothing can be done," you are not really saying, "There is nothing *I* can do."

Considerable advances have been made in the last decade, both in understanding of the pathogenetic mechanisms in acne and in treatment of the more severe forms. In the following review an attempt will be made to outline current concepts and practices in these two spheres, including, for completeness, a conventional clinical descriptive classification of the disease.

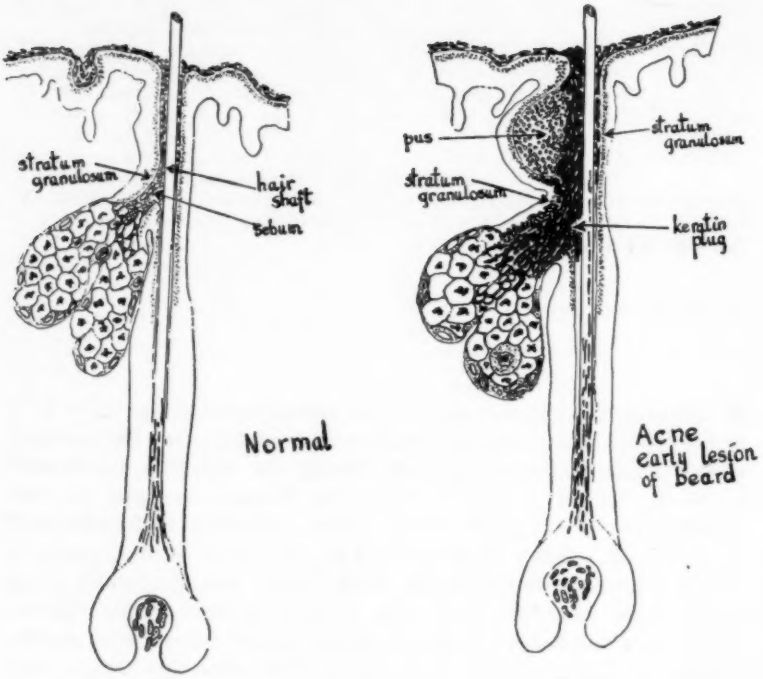

Fig. 31. *A*, Diagrammatic sketch of normal human hair follicle and sebaceous gland of skin of upper back. *B*, Diagrammatic sketch of early lesion of acne of human beard, showing hyperkeratinization of excretory duct of sebaceous gland with formed keratin plug and pocket of pus. Note that hair follicle below sebaceous duct is normal. Drawn from reconstructed scale model. (From Van Scott et al.: *J. Invest. Derm.*, Vol. 27.)

THE PATHOGENESIS OF ACNE

The Anatomic Lesions

The visible comedo at the pilosebaceous orifice is conventionally regarded as the primary anatomic lesion of acne. Van Scott's[30] painstaking tridimensional reconstructions of the normal and acne-involved pilosebaceous apparatus, however, indicate that the site of the earliest acne lesion is in the sebaceous gland duct, *before* it joins the follicular neck. The lesion consists of a hyperkeratotic thickening of the sebaceous duct wall which gradually encroaches upon its own lumen, producing varying degrees of obstruction to the outflow of sebum (Fig. 31). Subsequent upward extension of the keratotic plug so formed may involve and obstruct the follicular infundibulum. This appears to be a later phenomenon, so that the visible comedo is in fact the end-point, rather than the beginning, of the obstructive process.

In the course of its extension inspissated sebum and vellus hairs become incorporated in the plug, while focal accumulations of polymorphonuclear leukocytes may occur at any level, particularly in the lower portion of the follicular neck. The more superficial material becomes more densely packed, with eventual complete occlusion of the duct and follicle. Tears in the follicular epithelium may permit leakage of the irritative follicular contents into the dermis, where an inflammatory reaction may ensue. The nature of postacne scarring is determined by the severity and kind of inflammatory destruction and fibrosis of the dermis. When inflammation is deep and extensive, the overlying epidermis collapses into the dermal cavity, producing a depressed "saucerized" scar, whereas local inflammatory destruction followed by sloughing of the individual pilosebaceous unit results in the "ice-pick" kind of pitted scar.

Strauss and Kligman[24] state that the lesions of acne occur in a special "sebaceous follicle," which occurs on the face and, to a lesser extent, on the back and chest. These follicles are characterized by widely dilated follicular canals, large multilobular sebaceous glands and small, inconspicuous vellus hairs. A distinction is made between the "open comedo," which permits the continued discharge of sebum through a widely dilated orifice, and the "closed comedo," behind which dammed-up sebum may "explode" into the dermis. It is also claimed that breaks are constantly occurring even in the walls of sebaceous follicles uninvolved by comedones, allowing intradermal leakage of sebum. Strauss and Kligman re-emphasize the role of propionibacteria in enzymatically producing short-chain fatty acids from sebum: These acids may function not only as dermal irritants producing inflammation, but also as ductal and follicular irritants producing hyperkeratosis.

The primary lesions of acne, therefore, consist of (1) an obstructive plug in the duct of the sebaceous gland, (2) tears in the ductal or follicular epithelium, (3) inflammation within the follicle or within the dermis produced by irritative sebaceous material or bacteria, or both. The natural history of acne is a function of the immediate effects and late sequelae of these primary anatomic factors.

Most authors[1, 23, 25] stress the importance of sebaceous hyperplasia as a prerequisite for the developing acne lesions. It is suggested that glandular and ductal hyperplasia, however induced, forms the basis of the acne process. Certainly, sebaceous hyperplasia is temporally concomitant with the development of the acne process and is a prerequisite to hypersecretion of sebum.

The Conditioning Factors

Under this heading are included those factors which appear to condition or predispose the person to the development of the acne process.

GENETIC AND RACIAL FACTORS. It is a matter of repeated experience to observe the swarthy Latin mother and daughter showing evidence of past and present acne. Rothman[23] suggests that a high degree of sensitivity of the pilosebaceous apparatus to endocrine stimuli may be genetically determined, thus accounting for similar levels of hormonal stimulus producing in different persons a wide variety of target (pilosebaceous) response.

PILOSEBACEOUS PECULIARITIES. This category includes those anatomic or physiologic peculiarities of the pilosebaceous apparatus which are thought to condition the patient to the stimuli provocative of the acne process. Baer and Witten[1] point out that any anatomic peculiarity which obstructs or reduces the normal outflow of sebum may contribute to the acne process.

Many authors[1, 13, 20, 24] have drawn attention to the role of the growing hair as an important agent in maintaining a clear channel for conducting sebum to the surface. The strong terminal hair has been variously likened to a "rubber dam" or "broom" which facilitates free passage of sebum. On the other hand, a thin lanugo hair is said to be unable to maintain the patency of the follicular channel, thus providing a greater opportunity for keratinization to close the pilosebaceous orifice. Evidence supporting this hypothesis includes a positive correlation between the severity of acne and the ratio of lanugo to coarse terminal hairs in the comedo-involved follicles,[13] the production of exclusively vellus hairs by the "sebaceous follicle,"[24] and the fact that of the 46 acne-involved follicles studied by Van Scott,[30] 39 were found to be in the resting (telogen) phase, and only 7 in the proliferative (anagen) phase.

That the "rubber dam" concept cannot be the entire answer, however, is indicated by the finding[30] that, in the beard, the sebaceous duct maintains a separately compartmentalized channel all the way to the skin surface. The keratotic plug in this area remains confined to the excretory channel of the sebaceous duct. This observation minimizes the likelihood of the adjacent hair exerting any direct physical influence on the development of the comedo or its upward extension, at least in a bearded area. An alternative explanation[30] for which there is some evidence may be that cyclical quantitative or qualitative changes in sebum may accompany the growth cycle of the hair.

The Provocative Factors

In the presence of the appropriate conditioning influences factors included under this heading will either provoke the development of the anatomic lesions of acne or contribute to their progression.

ENDOCRINE FACTORS. Von Hebra,[15] in 1868, quoted Professor Rig-

ler, who lived in Constantinople, as saying that he had never seen acne in a eunuch. This was probably the first direct recorded observation linking acne and sex hormones, although scientific verification awaited the work of Bloch in 1931.[2] The onset of acne at puberty, the premenstrual exacerbation, and the development of acne lesions in women with masculinizing tumors, all suggest a provocative endocrine basis for acne. Experimental injections of testosterone have been shown[16] to induce acne lesions in predisposed persons. The approximately equal sex incidence invites the conclusion that adrenal cortical androgens are the important endocrine stimulus in female acne, but this is, at best, unproved. Women with ovarian agenesis do not have acne, although their adrenal cortices are presumably normal. A more credible explanation for which there is good experimental evidence[16, 32] is that progesterone plays the same acnegenic role in the female that testosterone does in the male. Both hormones (progesterone and testosterone) produce massive sebaceous hyperplasia when administered to spayed rats,[14] a finding paralleling the threefold increase in sebaceous gland volume occurring at puberty.

The precise *modus operandi* of the acnegenic hormones is speculative: The puberal sebaceous hyperplasia is well documented, but the question remains open as to whether the hormonal influence produces a biochemical change (Boughton et al.[3] found no change) in sebum which in turn irritates the glandular duct, or whether the hormone acts directly on the follicular duct, producing ductal hyperplasia and hyperkeratosis to initiate the acne process. Again the concept of genetic hypersusceptibility of the target organs to endocrine stimuli seems an inviting hypothesis.

The demonstration by Rothman's group[18] that the anterior pituitary contains a fraction, termed the "sebotropic fraction," in the absence of which sebaceous glands fail to respond to testosterone or progesterone, is highly significant. It would appear that there is yet another link in the acnegenic hormonal chain and therefore another point at which the chain may be broken. Rothman[23] speculates that the ultimate approach to acne therapy will be the use of a chemical inhibitor of pituitary sebotropic hormone secretion.

The production of typical acne lesions by chlorinated naphthalenes[27] applied externally (Halowax Acne) has led to speculation[23] that a particular chemical substance in sebum may be a provocative agent in acne. Boughton et al.[3] were unable, however, to distinguish any biochemical differences between sebum from normal and from acne patients.

Bacterial Factors. Although studies have been made on the organisms involved in the acne pustule, the exact role of bacteria in the acne process remains unclear. The frequent favorable response of

pustular and cystic acne to systemic antibiotics[28] suggests that bacteria may play an important role. Nevertheless the fact that organisms cultured from pustules which responded to antibiotics show sensitivities in vitro which bear no relation to clinical response[6] leads some authors[28] to suggest that antibiotics may have some role other than antibacterial. Alternative explanations are that though the organisms cultured have been aerobes, the provocative organisms are anaerobes, or that antibiotics eliminate sensitive microorganisms in distant foci of infection, the blood-borne products from which provoke the acne process.[25]

Mechanical and External Factors. In the "conditioned" person habitual manipulation, such as rubbing, stroking, squeezing or resting the face in the hands, may mechanically initiate the acne process by contributing to physical occlusion of the follicle.[11] A modern syndrome is "television acne," produced over the area covered by the hands upon which the hypnotized juvenile rests his chin. Occlusive (pancake type) cosmetics similarly produce follicular blockage and stasis of sebum, thus initiating the acne process.

Dietary Factors. That an individual patient's acne exacerbates after ingestion of a particular food is often incontrovertible. That many patients have been deprived of enjoyable and nutritious foods on grounds of vague impressions and hazy suspicions is equally incontrovertible. The main dietary factor upon which most dermatologists agree is chocolate. Whether this confection stimulates sebaceous secretion, abnormal sebaceous products or ductual hyperkeratosis is unknown. Hairless rats fed on a diet rich in chocolate[32] produced only broad smiles! In decreasing order of importance it may be worth while eliminating *on a trial basis* chocolate, nuts (including peanuts), cola drinks and sea foods. Reintroduction of each food at two-week intervals will give some idea of whether the elimination is worth while. Evidence that low fat or low carbohydrate diet reduces anything but body weight is lacking. Since iodides and bromides are themselves provocative of acneform eruptions, the use of iodized salt and bromide-containing medications is often interdicted. Trial elimination of the former may be worth while; the latter can always be avoided without hardship.

Emotional and Hyperhidrotic Factors. These are mentioned together because they probably belong together. There is good evidence that sebaceous gland secretion is not under direct nervous control,[8, 22] so that "stress" exacerbations of acne[31] must have some basis other than a "psychic seborrhea." The most likely explanation advanced seems to be that emotional hyperhidrosis rapidly emulsifies sebum, hyperhydrates the horny layer and contributes to incipient follicular occlusion—a "follicular prickly heat." This mechanism ap-

pears to be operative in the tropical acne syndrome,[26] in which the hyperhidrosis is thermal rather than psychic.

The contributory factor of manipulation[11] must always be considered in the anxious adolescent who increases the inflammatory component of his lesions by picking and squeezing. The excoriated acne of young women is a form of neurotic excoriations in a patient with pre-existing acne lesions available to traumatize.

THE CLINICAL PICTURE

Acne Neonatorum

Of particular interest to pediatricians is acne neonatorum, described by Kraus[17] in 1912. Commonly, the earliest lesions are milia-like, with subsequent development of erythema, follicular papules, and comedones on the cheeks. The typical acne lesions, which are usually present by the third month of life, rarely persist after the eighth month, when the condition subsides spontaneously. The lesions are smaller and set more closely together than those of juvenile acne vulgaris without the same tendency toward perifollicular inflammation.[12] The consensus is that the syndrome represents a true acne vulgaris of infancy in a highly predisposed subject (?target hypersusceptibility). Ninety per cent of the reported patients are males, all of whom have an abnormally high predisposition to severe acne vulgaris in adolescence.[12]

The syndrome of grouped comedones reported by Crocker in 1884[5] is thought[12] to have arisen from the external application of oils. There have been no case reports of group comedones since 1918.

Juvenile Acne

This type of acne, most commonly encountered by the pediatrician, usually first appears at puberty, although girls often present a year or so before this time. Juvenile acne has a characteristic distribution, involving the forehead, central parts of the face, chin, and the upper part of the chest and back. These are the areas of maximum sebaceous gland concentration prepuberally, and the areas most affected by the threefold puberal glandular enlargement (the lack of scalp involvement in acne again suggests the importance of the growing hair).

A satisfactory subclassification of juvenile acne is as follows:

Comedo acne, in which the comedo is the only visible lesion. The black surface discoloration is due to chemical oxidation, not dirt.

Comedo-papular acne (Fig. 32), showing, in addition to the comedones plugging the follicles, a mild to moderate perifollicular inflammatory response.

Fig. 32. Comedo-papular acne on the forehead of a 13-year-old girl. This stage may be regarded as the threshold of "clinical acne," since pure comedone acne is rarely presented to the physician as a major complaint.

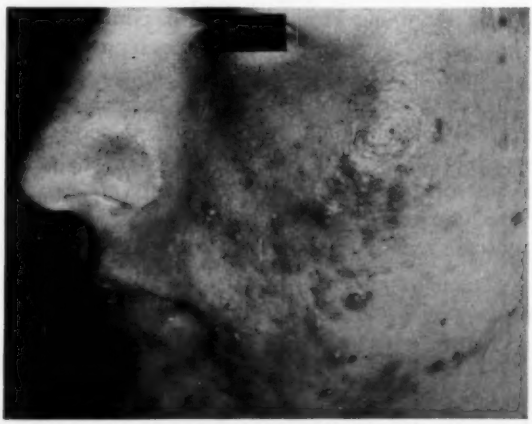

Fig. 33. Papulo-pustular acne in a 15-year-old boy. Although a range of lesions from comedones to early nodules is present, the predominant lesion is a papulo-pustule.

Papulo-pustular acne (Fig. 33). In this type of acne the follicular papule has a pustular head with a significant amount of perifollicular erythema and edema. The comedo may not necessarily be evident, since obstruction of the sebaceous duct was followed by clinical inflammation before the plug extended to the surface to become apparent as a comedo. The pustule is frequently sterile, at least to aerobic culture, and the accumulation of leukocytes and lymphocytes, intrafollicularly and perifollicularly, is probably the result of chemotaxis.

Fig. 34. Nodular acne in a 16-year-old boy. Note the absence of any visible comedone in most of these "blind" congested nodules.

Fig. 35. Nodulo-cystic acne in a 16-year-old girl. Drainage of these cysts, either by a wide-bore needle or the comedo extractor point, is indicated. Scar on right cheek arose from earlier scalpel surgery.

Nodular acne (Fig. 34), in which the predominant lesion is a hard, congested perifollicular nodule. There may, in addition, be papules and pustules, but the firm, blind, congested nodule is the predominant lesion. These nodules arise from early rupture of the sebaceous gland content into the dermis with subsequent severe deep and frequently long-lasting dermal inflammation. The tendency to persist for long periods without pointing or draining makes this lesion one of the more troublesome ones in acne. Again, it is uncommon to find a surface expression in the form of a comedone in relation to the nodule.

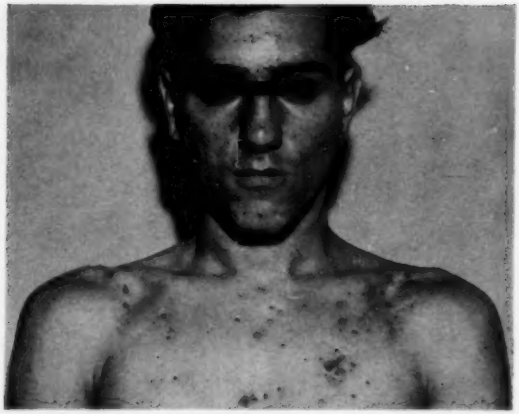

Fig. 36. Acne conglobata in a 15-year-old boy. Note the undermining and confluence of dermal cysts and abscesses on the chest; also the severe scarring that this process has already produced on the face.

Cystic acne (Fig. 35), presenting large cysts with puffy oily cores having little or no tendency to discharge to the surface. Cystic acne is a variant of nodular acne in which the major lesion becomes a cyst rather than a congested nodule.

Acne conglobata (Fig. 36) is characterized by large perifollicular abscesses which undermine, join up and sometimes ulcerate superficially. The large unsightly abscesses tend to extend over the neck, shoulders and upper portion of the back and chest. This most severe type of acne is thought to be associated with a developmental anomaly of the pilosebaceous apparatus and does not, therefore, strictly belong in the group of acne vulgaris.

For convenience acne vulgaris may be graded from I to IV: grade I, comedo acne; grade II, comedo-papular acne; grade III, papulo-pustular acne; grade IV, nodular and cystic acne.

Although it is frequently stated that acne clears up with marriage, copulation, and other sex-linked phenomena of "maturity," it is of interest to note that in a survey of 2500 soldiers[9] it was found that between the ages of 25 and 30, 21 per cent of the men had persistent acne, while between 30 and 39 years of age, 13 per cent of the men still had active clinical acne. Although it is true that acne *tends* to clear after adolescence, there is no guarantee that this will take place. The more severe the acne, the less the probability of clearing spontaneously at an early age and therefore the greater the necessity for early appropriate therapy.

A number of surveys have been conducted in an attempt to relate various factors to the development of the acne process. In a group of

2720 soldiers no positive correlation could be found between acne and dandruff.[4] (This is in contradiction to one of the most cherished notions on the subject of acne.) It is interesting to note that in this group of older men acne was found to predominate more on the trunk and less on the face, bearing out one's clinical impression that the upper portion of the back and chest is more affected in adults. A similar survey[7] found no association between acne, complexion, body hair, blood groups, height-weight ratio, ancestry or handedness!

MANAGEMENT

Ideally, the management of acne would consist in suppressing the principal provocative factors, thus preventing the appearance of the anatomic lesions. Although some progress has been made in this direction, it is still necessary to devote most therapeutic attention to controlling the progress of the obstructive phenomena and minimizing their consequences. The broad aim of management is to reduce cosmetic disability—presently in the form of active lesions, and subsequently in the form of scarring. Therapy may be local, involving the use of physical and chemical agents directly on the skin; systemic, including oral and parenteral medications; and general, embracing the management of the patient's diet, personal habits and emotional welfare.

Local Therapy

Topical medications offer the first best hope and in most instances will produce clearing without resorting to systemic therapy. All local therapy for acne is intended to produce, by chemical, physical or mechanical means, at least one of the following effects: (1) reduction of oiliness in and on the stratum corneum (i.e. "drying"); (2) controlled "peeling" of the stratum corneum; (3) removal of follicular plugs; (4) reduction in sebaceous gland secretion.

Chemical Therapy. Chemical agents used to produce these effects are sulfur, resorcin and salicylic acid, contained in creams and lotions, the drying effect of which is influenced positively by the alcohol content.

With the wide range of cosmetically adjusted lotions and creams commercially available it seems rather foolish to write "a la carte" prescriptions for daytime use. Many proprietary preparations are available in shades which most patients find more acceptable than the individual pharmacist's product. Nevertheless to maintain some individuality it is a good idea to write out a prescription for use at bedtime, when appearance is not so important (at least to juveniles!).

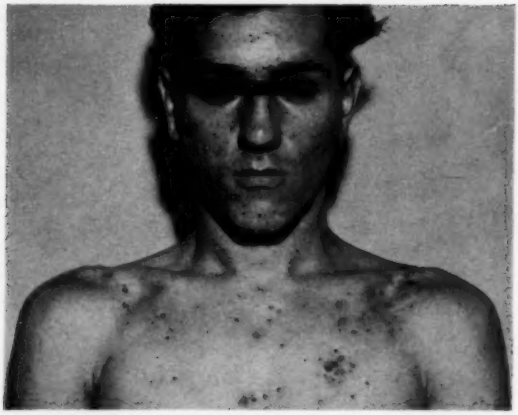

Fig. 36. Acne conglobata in a 15-year-old boy. Note the undermining and confluence of dermal cysts and abscesses on the chest; also the severe scarring that this process has already produced on the face.

Cystic acne (Fig. 35), presenting large cysts with puffy oily cores having little or no tendency to discharge to the surface. Cystic acne is a variant of nodular acne in which the major lesion becomes a cyst rather than a congested nodule.

Acne conglobata (Fig. 36) is characterized by large perifollicular abscesses which undermine, join up and sometimes ulcerate superficially. The large unsightly abscesses tend to extend over the neck, shoulders and upper portion of the back and chest. This most severe type of acne is thought to be associated with a developmental anomaly of the pilosebaceous apparatus and does not, therefore, strictly belong in the group of acne vulgaris.

For convenience acne vulgaris may be graded from I to IV: grade I, comedo acne; grade II, comedo-papular acne; grade III, papulo-pustular acne; grade IV, nodular and cystic acne.

Although it is frequently stated that acne clears up with marriage, copulation, and other sex-linked phenomena of "maturity," it is of interest to note that in a survey of 2500 soldiers[9] it was found that between the ages of 25 and 30, 21 per cent of the men had persistent acne, while between 30 and 39 years of age, 13 per cent of the men still had active clinical acne. Although it is true that acne *tends* to clear after adolescence, there is no guarantee that this will take place. The more severe the acne, the less the probability of clearing spontaneously at an early age and therefore the greater the necessity for early appropriate therapy.

A number of surveys have been conducted in an attempt to relate various factors to the development of the acne process. In a group of

2720 soldiers no positive correlation could be found between acne and dandruff.[4] (This is in contradiction to one of the most cherished notions on the subject of acne.) It is interesting to note that in this group of older men acne was found to predominate more on the trunk and less on the face, bearing out one's clinical impression that the upper portion of the back and chest is more affected in adults. A similar survey[7] found no association between acne, complexion, body hair, blood groups, height-weight ratio, ancestry or handedness!

MANAGEMENT

Ideally, the management of acne would consist in suppressing the principal provocative factors, thus preventing the appearance of the anatomic lesions. Although some progress has been made in this direction, it is still necessary to devote most therapeutic attention to controlling the progress of the obstructive phenomena and minimizing their consequences. The broad aim of management is to reduce cosmetic disability—presently in the form of active lesions, and subsequently in the form of scarring. Therapy may be local, involving the use of physical and chemical agents directly on the skin; systemic, including oral and parenteral medications; and general, embracing the management of the patient's diet, personal habits and emotional welfare.

Local Therapy

Topical medications offer the first best hope and in most instances will produce clearing without resorting to systemic therapy. All local therapy for acne is intended to produce, by chemical, physical or mechanical means, at least one of the following effects: (1) reduction of oiliness in and on the stratum corneum (i.e. "drying"); (2) controlled "peeling" of the stratum corneum; (3) removal of follicular plugs; (4) reduction in sebaceous gland secretion.

Chemical Therapy. Chemical agents used to produce these effects are sulfur, resorcin and salicylic acid, contained in creams and lotions, the drying effect of which is influenced positively by the alcohol content.

With the wide range of cosmetically adjusted lotions and creams commercially available it seems rather foolish to write "a la carte" prescriptions for daytime use. Many proprietary preparations are available in shades which most patients find more acceptable than the individual pharmacist's product. Nevertheless to maintain some individuality it is a good idea to write out a prescription for use at bedtime, when appearance is not so important (at least to juveniles!).

For the busy practitioner it would seem sensible to adopt a standard regimen containing a limited number of products with which he can become familiar. The following outline is presented with this concept in mind:

1. Instruct the patient to wash his face with toilet soap for five minutes three times daily: Acne-aid (Stiefel) or Fostex (Westwood), incorporating sulfur and salicylic acid, may be found more effective than regular soaps.

2. After each daytime washing apply *one* of the following: Fostril (Westwood): Tinted creme (sulfur, hexachlorophene, nonionic detergent) (this is exceptionally drying, and the maker's instructions to discontinue temporarily if drying or chapping is too severe should be heeded); Sulforcin (Texas Pharmacal): Clear lotion (sulfur, resorcin, pectin); Resulin (Almay): Tinted (three shades) lotion (resorcin, sulfur, alcohol); creme (resorcin, sulfur).

3. At bedtime apply the following cosmetically unattractive lotion:

Sulfur ppt	8%
Resorcinol	4%
Zinc oxide pulv.	20%
Talc	20%
Glycerin	15%
Isopropyl alcohol	
Aqua a.a. ad	100%

4. If any daytime medication produces too much drying, reduce the frequency of use. If the nighttime lotion is too drying, halve the concentrations of sulfur and resorcin.

PHYSICAL THERAPY. Electromagnetic radiation from the x-ray and ultraviolet portions of the spectrum has been used extensively in acne.

X-ray, the effect of which is to reduce sebaceous gland activity, is less used than previously, especially in the pediatric age group, in which its use seems unwarranted.

Ultraviolet radiation emitted by the cold quartz lamp is beneficial in producing a moderate peeling reaction. The hot quartz lamp, like natural sunlight, may be beneficially anti-acnegenic as an effective peeling and drying agent. If a patient purchases a sunlamp, he should carefully follow the maker's instructions for use. Particularly, going to sleep under a sunlamp is a hazard to be avoided.

MECHANICAL THERAPY. "*Acne Surgery.*" The use of a comedo extractor is simple and worth while. The essence of this art is gentleness; there is no point in doing roughly with an instrument what the patient could have enjoyed doing equally badly with his fingers.

The sharp end of the extractor is effective and less traumatic than a scalpel for puncture and drainage of nodular and cystic lesions.

Dermabrasion. Dermabrasion (planing) is not indicated in the juvenile or early adolescent period in which the acne process is still

active. This modality is intended to minimize the cosmetic disability produced by postacne scarring and should not be used at a time when all energies should be devoted to *preventing* such scarring.

Systemic Therapy

ANTIBIOTICS. The use of antibiotics in selected patients whose pustular, nodular or cystic acne has resisted topical therapy is worth while. As already mentioned, there is some speculation that their action may be other than strictly antibacterial.[1, 28] Tetracyclines are the drugs of choice, an easy-to-remember schedule suggested by Sulzberger[28] being this: 250 mg. 4 times a day for 4 days, 250 mg. 3 times a day for 3 days, and 250 mg. twice a day for 7 days. On completion of this course the minimum suppressive dose is determined.

When tetracyclines are poorly tolerated either by the patient or by the pocketbook, sulfisoxazole (Gantrisin—Roche) may be a suitable substitute on both counts. A similar regimen to that outlined for the tetracyclines is followed, individual doses being two to four times higher. If no response is apparent after the initial two-week course, it may be worth while changing the medication anyway: Patients responding little to sulfonamide may do better on an antibiotic. After obtaining a good result an effort should be made either to discontinue the drug or at least to find the minimum effective dosage.

Baer and Witten[1] have maintained patients on small doses (250 mg. of tetracycline daily) for months, and in some cases years, with gratifying results and with a minimum of side effects. Since these drugs are most effective in that variety of acne (pustular and nodulo-cystic) which is presently most disfiguring and subsequently most scarring, their use is most certainly worth a trial in acne of this type refractory to topical therapy.

ESTROGENIC HORMONE. On the basis of a postulated androgen-estrogen or progesterone-estrogen ratio disturbance and the experimental sebaceous hypoplasia induced by estrogen, this hormone has been used extensively in the treatment of refractory acne. With the advent of antibiotic therapy estrogen therapy is now usually confined to women with a definite history of premenstrual exacerbations, or to cystic acne in which antibiotics have been ineffective. The water-soluble conjugated estrogen Premarin is used in doses of 0.625 to 1.25 mg., beginning 18 days after the beginning of each menstrual period (or 10 days before the beginning of the next period) and continuing until the start of the next menses.

The paper of Torre and Klump[29] should be consulted for detailed indications for and contraindications to this regimen. A three-month trial is warranted: It has been shown that the recommended dosage

in male patients, even in the presence of gynecomastia, has no effect on the sperm count.[21]

THYROID HORMONE. On the basis of hypothyroidism producing disturbed keratinization with horny prominences at the follicular orifices, thyroid hormone has been used in the treatment of acne vulgaris. Although no connection has ever been demonstrated between acne vulgaris and hypothyroidism, as evidenced by protein-bound iodine and cholesterol levels, some experienced dermatologists maintain that a trial of tabs thyroid, ½ grain twice daily, may sometimes favorably tip the therapeutic scales.

VITAMIN A. This vitamin has been used therapeutically in most dermatoses associated with faulty keratinization. In conventional dosage of up to 50,000 International units daily, its use in acne is, at best, of dubious value. Lynch,[19] using doses of 100,000 units daily for 3 months, was unable to draw any favorable conclusions.

General Management

DIETARY MANAGEMENT. Elimination of chocolate, nuts and cola drinks is recommended. If the history suggests that any other items such as sea foods may play a provocative role, elimination should be on a trial basis followed by reintroduction and observation.

PSYCHIATRIC MANAGEMENT. Emotional problems in the patient with acne may be provocative of, secondary to, or incidentally associated with, the eruption. Failure to appreciate the significance of these problems may prejudice the results of an otherwise adequate therapeutic regimen.

At no age in the emotional development of the child is there such lability as in the teens. Violent fluctuations occur between dependency and independence, abstinence and indulgence, feelings of omnipotence and loss of self-esteem, indifference and heightened sensitivity. Because of this lability and sensitivity the secondary implications of acne may be most significant. Teenagers need to be taken seriously, and the teenager with acne needs to be taken even more seriously—especially by the physician. Specifically, acne often constitutes a severe blow to the narcissism of the individual. Capacity to handle this affront will be determined in large measure by the ability of the physician to provide supportive understanding and prognostic reassurance. Picking, squeezing, scratching and handling of the lesions are factors which, if ignored, may later prove difficult to control, since they may fulfill masochistic or symbolic functions.

The acne may be absorbed into the normal and abnormal psychology of the child *and* his family. It may become incorporated into feelings of guilt and need for punishment; feelings of shame and exhibitionism;

the need for close relations and the need to defend against these relations.

Limitations of time and experience will necessarily preclude the busy practitioner from undertaking any detailed analysis of the secondary and associated emotional factors in acne. If, however, it is apparent that such analysis would be beneficial to the patient, psychiatric referral in adolescence may avert an adult lifetime of maladjusted misery.

Awareness on the part of the physician that such emotional problems as have been briefly outlined do occur and require attention is important in the management of acne vulgaris.

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NATURE AND CAUSATION OF INSECT BITE REACTIONS

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Concern with the nature and degree of reactions of man to bites of blood-sucking insects has been overshadowed until comparatively recently by attention devoted to the role of arthropods in disease transmission. Before the demonstration of this role, around the turn of the century, few papers dealing with the bite reaction had appeared. Upon the realization of the importance of arthropods in the transmission of disease, somewhat more attention was paid to the bite reaction, but the literature has appeared sporadically and for the most part has been characterized by a lack of detailed studies.

During the past few years there has been an awakened interest in the bite reaction problem, as evidenced by reports of research activity among entomologists and workers in the medical field. Recently there has been an indication of a growing interest of clinicians in the reactions which may follow the bites of blood-sucking arthropods. Presumably this interest arises from an increased awareness of the clinical importance which these reactions may assume. As pointed out by Rook (see p. 817), many cases of papular urticaria, for which formerly a variety of causes have been suggested, are now believed to result from bites of insects, particularly fleas and bedbugs.

Published information on reactions to insect bites is widely scattered in a variety of journals, many of which are seldom if ever seen by the practitioner. The discussion which follows brings together the more pertinent information on the nature and causation of insect bite reactions. The references cited are intended to be representative rather than all-inclusive. As may be expected, many aspects of the reaction are considered, including theories offered to account for the reaction,

changes in reactivity resulting from repeated exposures to bites, specificity and desensitization.

FEEDING MECHANISMS

Skin reactions may result from bites by many kinds of insects, including mosquitoes, blackflies, biting midges, stableflies, deerflies, horseflies, fleas, lice and bedbugs. The mouth parts of these insects vary considerably from the needle-like type of the mosquito to the bladelike type of the blackfly. The former type is commonly inserted relatively deeply into the tissues of the host, while the latter is inserted more superficially, slashing the tissues and capillaries to obtain blood.

Workers at the Liverpool School of Tropical Medicine in England have made some interesting observations on the methods by which mosquitoes and other deep-feeders obtain blood meals.[16, 26, 27, 31, 52]

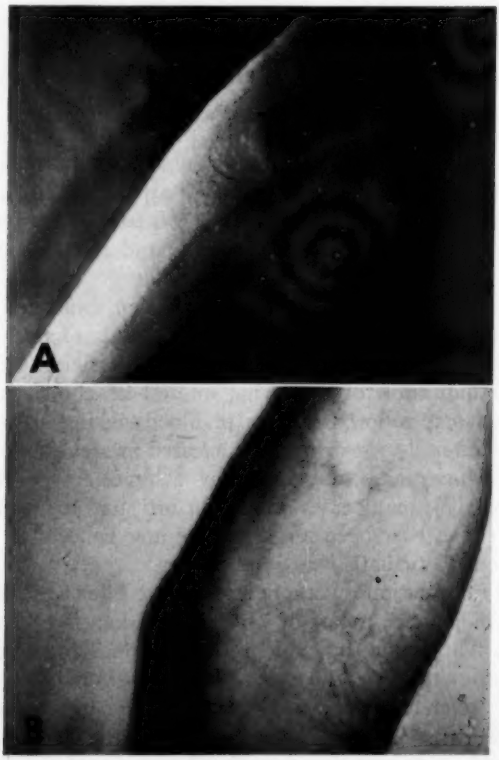

Fig. 37. Reactions to bite of *Aedes aegypti*. A, Immediate reaction; B, delayed reaction.

The distal portion of the needle-like fascicle was found to be actively flexible and to curve to permit penetration in almost any direction. Injections of saliva from the tip of the fascicle into the tissues of the host were observed to occur while the insect probed for blood. The finding of blood appeared to be accidental and was obtained by one of two methods, either directly from the capillary or indirectly by rupturing a small blood vessel and withdrawing blood from the resulting hemorrhage. It was noted that mosquitoes usually feed by the hemorrhage or so-called pool method, while bedbugs and cone-nose bugs commonly feed directly from the capillary.

Unless complicated by infection, the trauma resulting from the action of the mouth parts of any blood-sucking insect is seldom severe enough to cause any serious disturbance in the host.[28] Frequently the hemorrhage resulting from the surface wounds made by blackflies, stableflies and others, and less commonly from the pool method of deep-feeding insects, is readily discernible by gross inspection of the bitten area.

The cutaneous reactions which may follow insect bites are familiar. Shortly after the bite has been received a local swelling surrounded by a red flare usually develops, and this is frequently accompanied by itching. Figure 37, *A*, illustrates an *immediate reaction* to a mosquito bite. This reaction commonly disappears within an hour. Some hours later the bitten site may again become swollen and reddened. A delayed reaction to a mosquito bite is shown in Figure 37, *B*. When *delayed reactions* occur, the itching which nearly always accompanies them is usually far more intense and more lasting than the itching which develops about the time that the bite is received. Delayed reactions may cause insomnia, even prostration.

VARIATIONS IN SUSCEPTIBILITY TO BITE REACTION

People react differently to insect bites. Reactions will vary as to type, i.e. whether immediate or delayed or a combination of the two kinds. Reactions will also vary as to size and duration. A person may react in one way to the bites of one species and quite differently, or not at all, to the bites of another species. Some of the underlying causes of these variations will be discussed in the following pages.

The age of the subjects sampled is an important factor influencing the result likely to be obtained. None of the 10 children of 6 months to 3 years of age tested by Heilesen[43] reacted to bites of the yellow fever mosquito (*Aedes aegypti*). Three of nine newborn infants bitten in Rockwell and Johnson's studies[77] with this mosquito showed no reaction, while the remainder had only small delayed papules. Shaffer et al.[84] tested 30 persons of ages less than a year to 12 years for reactions to extracts of mosquitoes, fleas and bedbugs. They concluded that

urticarial reactivity to insect extracts is practically nonexistent during the first year of life, that the incidence of reaction increases rapidly and reaches a peak in the four-to-seven-year group, then tapers off at adolescence.

Reactions vary in size and in persistence. Some persons exhibit little reaction to insect bites throughout their life.[87] On the other hand, reports of serious effects are common in the literature. Cone-nose bugs (Hemiptera, Triatomidae) are the giants among blood-sucking insects. Their bites may produce severe pain accompanied by weakness and vomiting,[45] complete recovery occasionally requiring extensive periods.[53] Wood[94] records the histories of two subjects who were rendered unconscious by bites of a member of this insect group. Five of the seven patients mentioned by Micks[70] as having been treated for bites of *Triatoma* spp. suffered severe systemic reactions, anaphylactic shock occurred in two of these five patients, and one had fever and hemolytic symptoms. Serious reactions have also been recorded for tabanids,[24] bedbugs,[51] mosquitoes,[6, 9, 38] sandflies (*Phlebotomus* spp.)[29, 91] and biting midges (*Culicoides* spp.).[2]

An example of the seriousness of blackfly bites is given by West and Hudson.[92] Most children in the Baie Comeau region of Quebec, where blackflies are seasonally abundant, have marked reactions consisting in emotional distress and fatigue lasting for several weeks, mild leukocytosis and enlarged and hardened lymphatics, particularly of the posterior cervical chain.

The severity and persistence of the delayed reaction depend, in part, on individual susceptibility and, to a lesser degree, on the number of bites received. Some persons have a delayed reaction only if bitten by a large number of mosquitoes.

It has been recorded that receipt of additional bites occasionally will stimulate reactions at old bitten sites some time after the delayed papular reactions have disappeared. This reactivation of old bites was observed by Theodor[91] when several of his experimental subjects were bitten by sandflies. Heilesen[43] apparently observed the flareup of old mosquito bites on himself, but noted that this phenomenon was produced not only by later bites, but also by rubbing, or by application of heat to the skin in the vicinity of old bites.

CAUSATION OF THE REACTION

Opinions on the cause of reactions to insect bites have differed. These opinions may be summarized as follows:

(a) The reactions to insect bites are the result of a nonspecific irritation caused by a toxic substance which insects inject while feeding.

(b) The reactions are the result of a nonspecific irritation and a specific sensitization to the injected material.

(c) The reactions are the result of specific sensitization, and if toxic substances are included in the injected fluid, they fail to produce any significant effect.

Reactions Caused by Toxicity

The toxicity theory was proposed as long ago as 1738 by Réaumur.[13] In 1904 Schaudinn[83] postulated that the reaction to the mosquito bite was caused by carbonic acid formed by enzymes of yeast cells supposedly contained in the diverticula of the mosquito's esophagus. Several workers have reported that emulsions of whole insects or of salivary glands produce toxic reactions in man and experimental animals.[10, 25, 32, 44, 67] According to Hartman,[33] fleas produce skin reactions by injecting either an "H-substance" or more probably a complex toxin which causes cellular destruction and liberates H-substance. Toxic reactions to mosquito extracts, causing death of guinea pigs, have been reported by Rockwell and Johnson.[77] Nevertheless in studies carried out by McKiel[62, 63] and A. Hudson et al.[46] several hundred rabbits and more than a hundred guinea pigs with no previous contact with mosquitoes were injected with mosquito extracts, or exposed to bites of several species of mosquitoes, without exhibiting any initial reactions.

Reactions Caused by Toxicity and Allergy

Results obtained in their early work led Gordon and Crewe[27] to conclude that immediate and delayed reactions to insect bites have separate causes, an acquired sensitivity to the injected fluids being responsible for the former and a slow-acting toxic substance being responsible for the latter. As a result of subsequent work this conclusion was modified, however, and the theory that an injected toxic substance participated in the reaction was discarded.[30]

Eckert et al.[18, 19] attributed the delayed reaction to previous sensitization because it may be removed by desensitization procedures. The immediate reaction, on the other hand, was believed to be caused by histamine, which the mosquito injected while probing and feeding. The extent to which the immediate response develops was believed to depend upon the host's susceptibility to histamine. Eckert's theory is untenable for the following reasons:[63]

(a) Rabbits previously sensitized to mosquito bites by injections of mosquito extract, or exposures to mosquito bites, fail to exhibit skin reactions when injected intracutaneously with microgram quantities of histamine.

(b) Rabbits can be sensitized to mosquito bites by means of injections of mosquito extract previously dialyzed for 48 hours against flowing water, a process which removes all low molecular weight material, including histamine.

(c) There were substantial errors in the technique of Eckert et al.

Histamine has been identified in extracts of blackflies by Hutcheon and Chivers-Wilson,[50] but these authors concluded that reactions to bites of blackflies appear to be the result of other factors in the salivary secretion.

In our opinion there is no substantial body of evidence to indicate that toxicity regularly plays a role in reactions to insect bites. Such toxic effects as may result are of infrequent occurrence and probably can be explained as resulting from other factors than the injection of salivary fluids.

Reactions Caused by Allergy

The theory that allergy is the underlying cause has gained support in recent years and is now almost universally accepted. Although Rockwell and Johnson[77] regarded toxicity as a contributory cause, they believed that allergy plays the more important role.

Evidence favouring allergy as the responsible mechanism has accumulated gradually and comes from the following sources: (*a*) sequence in which reactivity to insect bites develops in the individual; (*b*) passive transfer of sensitivity; (*c*) experimental sensitization of animals.

Sequence in Development of Reactivity. Instances in which persons have been found who exhibit no reaction to mosquito and flea bites are given in Tables 9, 10 and 11. Such studies are usually hampered by an unknown factor: namely, the extent of previous exposure to the test insect or to closely related insects. This unknown factor is minimized in very young children and eliminated entirely in the newborn infant. Nevertheless, because of its sensitivity to trauma, the skin of the infant may itself introduce a problem in interpreting reactivity. Studies in which young children have shown no reaction to bites of particular insects have been mentioned earlier.[43, 49, 77, 84]

Several workers have studied the effects of repeated exposures to insect bites in order to observe changes in the nature of the reaction.

Kemper[51] has reported observations on his own reactions to bedbug bites during an 11-month period of repeated exposures. At the beginning of the experiment only a papular delayed reaction developed, and this did not appear earlier than 24 hours. While receiving 30 bites on the same area of the forearm every third day, he noted that the interval between bite and reaction gradually decreased from 24 hours to zero. Coincident with this change in the latent period, an increase in the

size of the cutaneous reaction at first occurred, followed by a gradual decrease until finally, during the eleventh month, no reaction to the bites developed. In summary, Kemper's reaction progressed from the delayed type, to the immediate type, to the refractory state.

Other investigators have usually observed that there is a period during which a distinct immediate and a distinct delayed reaction occur. Theodor[91] studied the change in reactivity of subjects whose initial reaction to sandfly bites was of the delayed type. This reaction to these bites appeared at various intervals up to 34 days, after the first exposure. With further exposures small, immediate, white wheals developed. These disappeared completely within an hour and were followed later by delayed reactions.

A similar study was carried out by Mellanby[69] in England, using A. *aegypti*. He selected a group of students who could not have been exposed previously to this mosquito. When the experiment was begun, the first reaction appeared 24 hours after the bites had been received. After several exposures an immediate reaction also occurred along with a reduction to two hours in the latent period preceding the delayed reaction. With further exposures immediate reactions continued to occur, whereas delayed reactions became less severe and eventually disappeared entirely. Mellanby suggested that continued exposures would cause the immediate reaction also to disappear.

These observations on the effects of repeated exposures to bites, together with the results of the previously mentioned sensitivity tests on children, indicate that a series of stages in acquisition and later loss of reactivity to insect bites may be expected as a trend. Table 7 lists these stages. Part of this trend is illustrated by our observations[66] on the natural evolution of reaction types in a boy (DM) in response to A. *aegypti* bites (Table 8).

Subject DM was first bitten by this mosquito when he was three years of age. At that time he was in stage II (−, +). Approximately one and a half years later (two seasons' exposure to indigenous mosquitoes) he was found to be in stage III (+, +). The delayed reaction had become more notable, but of shorter duration. He was still in stage III seven years after the initial test, but since his delayed reaction had almost completely disappeared and the immediate type had increased, it is

TABLE 7. *Stages in Acquisition of Insect Bite Sensitivity*

STAGE	IMMEDIATE REACTION	DELAYED REACTION
I	−	−
II	−	+
III	+	+
IV	+	−
V	−	−

TABLE 8. *Reactions of Subject DM to* A. Aegypti *Bites*

SUBJECT'S AGE	TEST EXPOSURE	IMMEDIATE REACTION	LATENT PERIOD	DELAYED REACTION
3 years.....	5 bites, right arm 48 bites, left arm	Negative	21 hours	Papules 1–2 mm., lasting 8 days Erythema 5 days Pruritus absent
4½ years.....	2 bites, right arm 1 bite, left arm	Wheals 4 mm. Erythema absent Pruritus absent	12 hours	Papules 9–15 mm., lasting 2 days Erythema 12 hours Pruritus intense, lasting 8 hours
11½ years.....	2 bites, right arm 1 bite, left arm	Wheals 5–6 mm. Erythema 8 mm. Pruritus moderate, lasting 20 min.	12 hours	Papules 2 mm., lasting 18 hours Erythema absent Pruritus absent

apparent that he had progressed closely to stage IV (+, —). Case histories obtained in this manner to show the changing reaction of children to bites of a known species of insect, preferably with test exposures beginning shortly after birth, could provide valuable data necessary to a better understanding of reactions to insect bites.

The trend described above for insect bite sensitization has been observed in allergies to other substances. Tezner[90] found that repeated intracutaneous injections of ovalbumin in human subjects produced at first no reaction. Later, after several injections, the delayed reaction appeared, followed still later by both immediate and delayed reactions. Finally, the immediate reaction alone occurred. Mote and Jones[72] observed the same sequence of changes in skin reactions to horse serum as patients became hypersensitized, and noted further that sensitivity to horse serum was lost in the reverse order when injections were discontinued. Salvin[80] reported that injections of small amounts of ovalbumin or diphtheria toxoid into guinea pigs produced delayed reactions several days before Arthus-type (immediate) sensitivity or serum antibodies could be demonstrated. These observations have been interpreted by Tezner, Mote and Jones, and Salvin, as indicating that delayed hypersensitivity is an early, immature stage in the immune process. The peak or mature stage in the acquisition of hypersensitivity therefore would be manifested by the immediate type of skin reactivity.

Benson[6] postulated that separate antigens are responsible for delayed and immediate reactions. De Meillon[15] shared this view, but suggested that the antigen causing the delayed reaction is probably of universal occurrence, since delayed reactions may be seen in the supposed absence of prior insect bites. Failure to find delayed hypersensitivity to haptens such as picryl- or acetyl-groups of protein conjugates at any time before antibodies were produced led Benacerraf and Gell[3] to

favour the theory that immediate and delayed types of hypersensitivity are separate and distinct processes directed against qualitatively different groups or areas on the antigenic molecule. Results of studies on the anamnestic response of guinea pigs to a variety of protein conjugates have been interpreted by Salvin and Smith[81, 82] as supporting their earlier conclusion that delayed hypersensitivity is an immature stage in the immune process. Although this hypothesis cannot yet be regarded as proved, it more readily answers some of the questions about hypersensitivity to insect bites.

Passive Transfer of Sensitivity to Insect Bites. The allergic nature of the bite response has been further substantiated by several studies in which passive transfers have been made. Successful transfers of the immediate type of sensitivity have been made between human subjects, using the yellow fever mosquito,[77] the malaria mosquito (*Anopheles maculipennis*)[39] and the bedbug (*Cimex lectularius*).[40] Successful transfer of insect bite sensitivity between experimental animals appears to be more difficult.[17, 27, 62]

Transfer of delayed reactivity has not been successful.[39] An attempt by Hecht[40] to reduce the delayed reaction to insect bites in a subject hypersensitive to *An. maculipennis* by injection of serum from a person who had only an immediate reaction failed. Apparently a similar test carried out by Brown et al.[9] and involving hypersensitivity to *A. aegypti* bites was successful.

Sensitization of Experimental Animals. The demonstration that laboratory animals, normally nonreactive to insect bites, can be rendered hypersensitive by injections of insect extracts or exposures to insect bites has provided conclusive proof of the allergic nature of the reaction.[4, 5, 17, 46, 48, 62, 63]

The skin reaction to mosquito bites in animals previously sensitized by one of these methods differs in certain respects from that of sensitized human subjects. The erythema, frequently so striking in the human being, is nearly absent in the animal. Also the wheal is slower in making its appearance and likewise slower in disappearing. Though subject to variation, the wheal in the rabbit, guinea pig or rat begins to appear within 10 to 15 minutes of the bite, reaching a maximum in one hour. In some rabbits the wheal is long-persisting (Arthus reaction). Delayed reactions, distinctly separated from the immediate reaction, have never been observed in our tests with mosquito bites.

Reactions of experimental animals to bites of other insects may differ from these observations. For example, Hudson et al.[48] have reported that guinea pigs which were sensitized to flea bites had delayed reactions which reached maximum size in 24 to 48 hours and subsided in 2 to 7 days. Immediate reactions were not seen. In later studies by this group[5] it was determined that delayed hypersensitivity in guinea pigs

developed after five to seven days of daily exposure to flea bites. Immediate reactivity was noted after an additional two to seven days of exposure. When sensitivity was induced by means of injections of flea extracts, the latent period preceding the delayed reaction extended from 10 to 14 days, the immediate reaction again appearing 2 to 5 days later. Sensitivity of these animals never progressed beyond stage III even after repeated exposure for several months.

INCIDENCE OF REACTION TYPES

The type of reaction which may develop in an individual subject after an insect bite will depend on several factors, including the degree of previous exposure to that insect, and possibly to other insect antigens, as well as on the relative ease with which that person tends to become hypersensitive.

Tests to determine types of reactivity to A. *aegypti* bites have shown that most people have a skin reaction even though never before bitten by that species.[43, 66, 73, 77] Results are given in Table 9. The incidence of reactions of persons bitten by the human flea (*Pulex irritans*), a fox

TABLE 9. *Reactions Exhibited by Adult Subjects to* A. Aegypti *Bites*

REACTION		HEILESEN[43]			ROCKWELL AND JOHNSON[77]			O'ROURKE AND MURNAGHAN[73]			MC KIEL AND WEST[66]		
Immediate	Delayed	No.	Per cent		No.	Per cent		No.	Per cent		No.	Per cent	
−	−	6	19		5	9		6	17		6	3	
−	+	6	19	48	2	4	81	5	14	20	11	5	64
+	+	9	29	61	44	77	88	2	6	70	125	59	92
+	−	10	32		6	11		23	64		69	33	
Total		31			57			36			211		

TABLE 10. *Reactions Exhibited by Children under 10 Years of Age to Bites of Fleas* (P. Irritans, P. Simulans *and* C. Felis)[49]

REACTION		P. IRRITANS			P. SIMULANS			C. FELIS		
Immediate	Delayed	No.	Per cent		No.	Per cent		No.	Per cent	
−	−	1	4		6	17		11	34	
−	+	15	48	96	22	63	80	14	44	63
+	+	15	48	48	6	17	20	6	19	22
+	−	0	0		1	3		1	3	
Total		31			35			32		

TABLE 11. *Reactions Exhibited by Subjects (10 Years and over) Bitten by Fleas (P. Irritans, P. Simulans and C. Felis)*[49]

REACTION		P. IRRITANS			P. SIMULANS			C. FELIS		
Immediate	Delayed	No.	Per cent		No.	Per cent		No.	Per cent	
−	−	24	41		31	52		30	58	
−	+	22	37	57	17	28	43	15	29	38
+	+	12	20		9	15		5	9	
+	−	1	2	22	3	5	20	2	4	13
Total		59			60			52		

flea (*P. simulans*) and the cat flea (*Ctenocephalides felis*), as compiled from data given by Hudson et al.,[49] is shown in Tables 10 and 11. Although the incidence of types of reactions reported by different authors in tests using mosquitoes varied, and variation between species was recorded in tests with fleas, two trends seem apparent, at least as they apply to the species used: (*a*) that a higher proportion of those tested reacted to bites of the mosquito than to bites of the fleas, (*b*) that the more common reaction to bites of the mosquito is the immediate type, while the delayed type predominates in response to flea bites.

SPECIFICITY OF BITE REACTIONS

The practitioner may be asked this question: "If I react strongly to bites of one insect species, am I likely to react in a similar way to bites of other species?" Published literature contains several observations on this point, but few detailed studies have been made.

A high level of specificity was noted by Hase[34] in a person who had a strong immediate reaction to bites of the common bedbug (*Cimex lectularius*), but failed to exhibit any definite immediate reaction to bites of another bedbug (*C. rotundatus*).

Complete cross-sensitivity to three species of fleas was noted by Hudson et al.[48, 49] in specificity tests on human beings and experimental animals. Frequently, one or more differences in reaction are found when cross-reactivity occurs.[9, 41, 42, 48, 69, 77] The results of specificity tests in human subjects shown in Table 12 illustrate this point.[63] The extreme variability of reaction was also observed in tests on animals sensitized by exposures to only one insect species.[46, 48] The degree of sensitivity to heterologous species appears to be determined by the extent of prior exposure to biting insects or time during the sensitization period at which the test is made, specificity being higher during the early stages of sensitization.[8, 46]

TABLE 12. *Comparison of Reactions in Human Subjects to Bites of Various Mosquitoes*

SUBJECT	MOSQUITO	IMMEDIATE		DELAYED	
		Wheal	Flare	Degree	Duration
HM	*A. aegypti*	3.6 mm.	0 mm.	+	1 day
	A. atropalpus	0	0	+	1 day
LA	*A. aegypti*	14.7	57	−	−
	A. atropalpus	9.9	43	−	−
MA	*A. aegypti*	9.3	45	−	−
	A. atropalpus	3.8	27	−	−
	A. vexans	6.2	40	−	−
	C. pipiens	2.7	6	+	1 day
RD	*A. aegypti*	2.5	5	++	5 days
	C. pipiens	3.0	6	−	−
RP	*A. aegypti*	2.5	0	+++	10 days
	C. pipiens	2.6	5	−	−
TW	*A. aegypti*	10.6	44	−	−
	A. atropalpus	5.9	27	−	−

CHARACTERISTICS OF THE SUBSTANCE RESPONSIBLE FOR BITE REACTIONS

Extracts of whole insects commonly used in performing skin tests and in attempting desensitization are complex mixtures of numerous components, many of which probably play no part in the bite reaction. Characterization of the active ingredients and fractionation methods for separating these from the extraneous materials are problems of practical importance to the clinician. Only meager information is available.

The substance responsible for eliciting skin reactions in persons hypersensitive to mosquito bites has been shown to be present in a number of different organs of the mosquito.[14, 37, 57, 77] Only the salivary glands caused both immediate and delayed reactions, according to Hecht.[37] Salivary gland material produced greater reactions in sensitized hosts than did organs from the abdominal region in a comparison made by de Buck.[14] Nevertheless the opposite effect was observed by Rockwell and Johnson[77] in tests comparing head-thorax with abdomen antigens. Extracts of the head-thorax region and of the abdominal portion of mosquitoes were tested by McKiel[63] for their capabilities of sensitizing laboratory animals to mosquito bites. Only the head-thorax extract produced this condition. This and other observations led McKiel to conclude that the substance which is capable of inducing sensitization to mosquito bites is restricted in its occurrence to the head-thorax region, probably the salivary glands, while the fraction which is active in eliciting skin reactions is distributed throughout the body of the mosquito.

Proof that the activity of the fluid injected by the feeding tsetse fly originates in its salivary glands was obtained by Lester and Lloyd.[54] Bites of flies from which the salivary glands had been removed surgically failed to cause skin reactions in bite-sensitive persons. Evidence that the bite-reactive material originates in the salivary glands of the mosquito has been reported recently by Hudson et al.,[47] who showed that cutting the salivary duct of the mosquito does not prevent it from feeding, but does eliminate the skin reaction to its bite.

The skin-reactive material of the mosquito is water-soluble and non-dialyzable.[6, 64] It can be precipitated by cold alcohol, cold acetone or ammonium sulfate.[6] Most of the active components are precipitated with 88 per cent acetone.[77] The skin-test antigen is thermostable, resisting boiling for 25 minutes.[64] Acidification before boiling increases its heat resistance.[6] Boiling for one hour reduces the activity by about one-half.[77] It appears that the sensitizing antigen is more sensitive to heat than the skin-reactive component, at least as it affects laboratory animals.[63]

Various authors have suggested that the insect salivary secretion consists of more than one component.[12, 22, 55, 85] Recent histologic and histochemical studies of mosquito salivary glands by Orr et al.[74] confirm earlier suggestions that the glands may produce different chemical substances. Three principal regions with secretory activity were demonstrated, together with evidence that each of these regions elaborates one or more secretory products. It appears that (*a*) a mucopolysaccharide is probably produced in the central lobe of the gland, (*b*) a carbohydrate-protein complex as well as an enzyme is produced in the body of the lateral lobes, and (*c*) a neutral mucin and an acid protein are produced in the necks or basal portions of the lateral lobes.

Benjamini et al.[4] found that the oral secretion collected from cat fleas by feeding them through a membrane on distilled water will sensitize guinea pigs only if combined with Freund's complete adjuvant. They interpreted this observation as indicating that the sensitizing component of the flea secretion is haptenic.

Whereas it is only the female mosquito which feeds on blood (males being satisfied with a diet of nectar from flowers), an extract of male mosquitoes has been shown to be capable of producing skin reactions and of sensitizing experimental animals.[6, 63]

DESENSITIZATION

Reports in the literature indicate that at least some persons lose much of their sensitivity through prolonged contact with insects. During World War I, Hase[34] had the opportunity of observing the reactions of large numbers of soldiers to bites of the body louse (*Pediculus humanis*

corporis). The numbers which lost their sensitivity approximated those who remained sensitive. Theodor[91] stated that persons in Palestine, continuously exposed for years to sandfly bites, eventually ceased to react.

Reference has been made already to Kemper's experiment[51] on the effects of repeated exposures to bedbug bites in which he was successful in sensitizing and later desensitizing himself.

According to Morse,[71] English and Irish immigrants newly arrived in the United States frequently came under the physician's care because of reactions to mosquito bites. He mentioned two persons who ceased to be troubled after having been in America, one for two years and the other for seven years. Belief in the theory that prolonged contact with mosquitoes will result in a reduction of reaction was held by Bowen,[7] McKinely[67] and Gordon and Crewe.[27] Martini[58] observed no reduction in wheal size, however, after several weeks of exposure to *A. aegypti*. None of the seven subjects repeatedly exposed to *A. aegypti* bites by McKiel and West[65] showed any changes in the immediate reaction. Delayed reactions were reduced in two of the subjects, however, and eliminated entirely in a third volunteer.

Numerous workers have used insect extracts in attempted desensitization (hyposensitization), with apparently varying degrees of success. Of 128 patients treated for flea bites by Cherney et al.[11] and McIvor and Cherney,[59, 60] 113 reported having experienced a reduction in size and duration of the wheals and decreased pruritus. Hatoff[36] treated 129 infants and children for reactions to flea bites. Of these, 78 per cent were benefited, the results in 5 per cent were equivocal, and 17 per cent failed to respond. On the other hand, Hartman[33] stated that he had tried flea extracts prepared by every means described in the medical literature up to the end of 1944 and had obtained ineffective results.

Mease[68] was able to relieve the strong reactions of a patient hypersensitive to bites of the deerfly (*Chrysops discalis*). Only transient wheals resulted from bites received after a course of injections of deerfly extract.

A number of patients treated by Benson[6] for reactions to mosquito bites showed decreased delayed reactions, while immediate reactions remained unchanged. A single injection of antigen concentrated by precipitation with cold alcohol was effective in relieving one patient of delayed effects for four seasons. Only temporary benefits were obtained in desensitization attempts reported by Brown et al.,[9] Heilsen[43] and Rockwell and Johnson.[77]

Laboratory animals have been used to study the efficacy of desensitization procedures against the immediate form of reactivity. Attempts using subcutaneous injections of graded doses of antigen in rabbits by

TABLE 13. *Effect of Intravenous Injections of* A. Aegypti *Extract on the Bite Reaction of* Aegypti*-Sensitive Rabbits*

DAY OF EXPERIMENT	DIAMETER (MM.) OF WHEAL IN RABBIT No. 1	No. 2	No. 3	No. 4
1 (A.M.)	5.8	5.6	4.2	4.8
1 (A.M.)	Injected 2 ml. extract I.V.			
1 (P.M.)	0	0	0	0
2	3.1	4.7	2.3	4.5
3	4.0	4.6	4.5	3.3
4	4.5	4.9	3.7	4.3
6 (A.M.)	5.4	5.4	4.7	4.6
6 (A.M.)	Injected 2 ml. extract I.V.			
6 (P.M.)	0	0	0	0
7	0	4.2	2.0	4.3
8	3.3	5.2	3.1	4.8
9	4.0	5.7	3.8	4.9
13	6.4	5.8	4.8	5.6

Dubin et al.[17] and McKiel and West[65] were unsuccessful even when the injections were given over periods as long as 49 days.

The effect of injection of mosquito extract by the intravenous route has been studied in hypersensitive rabbits.[65] Pertinent data are shown in Table 13. On each of the two occasions in which intravenous injections were made, all four rabbits were found to be refractory to challenge bites three hours after the injections. Sensitivity returned, however, during the next day or two. These results were confirmed in an additional test involving 13 *aegypti*-sensitive rabbits (one of which died of anaphylactic shock). Three of the survivors remained nonreactive for five days, but reacted on the seventh day. Similar results were obtained in other tests utilizing extracts of other mosquito species (*A. atropalpus, C. pipiens*) to desensitize *aegypti*-sensitive rabbits.

Evidently, even a procedure as drastic as intravenous injection renders sensitized rabbits refractory to mosquito bites for only brief periods. The finding that extracts of heterologous species of mosquitoes will also desensitize indicates that this process is less specific than sensitization. This is in agreement with Rockwell and Johnson's report[77] of a patient who became desensitized to the delayed effect of *C. pipiens* bites after subcutaneous injections of *A. aegypti* extract.

The most notable feature of the reports concerning attempts to desensitize patients suffering from reactions to insect bites is the conflict in the claims. It seems safe to assume that part of the reason for failing to obtain more uniform results lies in the investigator's dependence on the subjective assessment by the patient. It has been the experience of Hudson and co-workers[49] that many patients never see the insect responsible for the clinical condition except in cases involving biting flies. "Fleas" brought to their clinic by patients as evidence of the

identity of the troublesome insect were proved to be "anything from grain beetles to small weed seeds." Possibly some of the unsuccessful attempts have been due to injection of the wrong insect antigen. Hudson also suggests that reported relief of flea bite symptoms may be due in certain instances to a seasonal decline of flea populations. How much of the apparent beneficial effects in reality have been due to desensitization and how much should be attributed to normal variation in the way the person reacts on different occasions are questions which must remain unanswered for the present. The specificity of the reaction can also create false impressions in respect to desensitization. The species of mosquitoes which are common in early spring usually are not the same ones which are common in midsummer. The manner in which a person reacts to some of the early spring mosquitoes is often very different from the way he will react to some of the late arrivals, apart from any acquired loss in sensitivity due to recent exposure. *Culex* mosquitoes appear later in the season than do *Aedes*. Differences in reactions to these two groups are illustrated in Table 12.

Although one or more of these sources of error undoubtedly have influenced the conclusions reached, there is general agreement with Sulzberger's observation[89] that patients can be desensitized with comparative ease so far as the delayed reaction is concerned, but the immediate reaction is difficult to influence and usually remains constant in spite of desensitization procedures.

The explanation for the relative ease with which the delayed reaction may be decreased in intensity, or even eliminated, may be found in the suggestion referred to earlier that the delayed reaction is an immature stage in the acquisition of sensitivity. According to the scheme shown in Table 7, continued exposure to the offending allergen will frequently change the reaction to the "immediate only" stage, i.e. stage IV. Immediate reactions, even strong ones, are of fleeting duration. Delayed reactions, on the other hand, may be long-persisting and extremely painful. A method of treatment which converts a patient's reaction from the severe delayed to the immediate type is certainly beneficial.

Possibly greater benefits would be derived if improved methods of preparing the extract for treatment of clinical cases could be found. Obviously, a saline extract of whole insects is a crude preparation. Studies on methods of purifying such extracts appear essential before greater benefits from attempts to desensitize are likely to be seen.

SYMPTOMATIC TREATMENTS

A variety of nonspecific treatments for bite reactions has been recommended, including intravenous procaine hydrochloride,[7] local injection

of epinephrine,[7, 9, 33] oral magnesium chloride[56] and topical use of calamine lotion, aqueous carbolic acid or an alcoholic solution of menthol.[23] Shannon[86] reported that thiamine chloride was effective both in repelling mosquitoes and in relieving bite reactions when this vitamin was administered orally or subcutaneously, but not topically. Good results were also claimed by Eder[20] in treating flea bite reactions with thiamine chloride. Wilson et al.[93] failed to substantiate these claims either as a repellent or as a curative measure and further stated that similar findings were obtained by workers in the United States Department of Agriculture and the National Institutes of Health of the United States Public Health Service. Rockwell and Johnson[77] found that cortone decreased delayed reactions to mosquito bites in one of five patients treated. Two others showed decreased reactions after receiving ACTH.

Various antihistamines have attracted interest as possible methods of relieving reactions to mosquito bites. When taken orally, antihistamines have relieved pruritus,[79] but otherwise do not reduce the reaction.[27, 29, 77] Antihistaminic creams and ointments are of value in relieving pain from mosquito bites, according to Straus,[88] Bowen[7] and O'Rourke and Murnaghan.[73]

Unfortunately, all these claims have been based on results seen in too few subjects. When details of method used in testing antihistaminic creams have been given, they have been found to be open to serious criticism such as failure to remove bias of subject and evaluator by inclusion of a control cream and by failure to randomize the site to be treated. Carefully controlled tests on 146 volunteers by McKiel et al.[61] failed to show any benefit of Pyribenzamine cream applied topically either before or after mosquito bites were received. The volunteers reported relief of pruritus at sites treated with the control cream (Dermabase) as frequently as at sites treated with the antihistaminic cream.

Mosquito bite-sensitive rabbits have been used by McKiel[62] to test the effect of a subcutaneously injected antihistamine (Benadryl) on the bite reaction. The minimum effective dose for significant suppression of whealing was found to be 2.7 mg. per kilogram. Although this is a larger dose on a weight basis than is recommended for man, it suggests that internally administered antihistamines might be useful in alleviating mosquito bite reactions.

Other nonspecific treatments tested in rabbits[62] included injections of Mecholyl according to Pearson's method,[75] intravenous histamine under the protection of Benadryl according to the procedure used by Ambrus et al.,[1] and hapamine desensitization as used successfully by Hartman[33] for flea bites and by Riek[76] for dermatitis caused by *Culi-*

coides (midge) bites. None of these methods effected a significant reduction in mosquito bite wheals.

SUMMARY

Sufficient evidence is now at hand to state definitely that the reaction to the bites of blood-sucking insects is caused by an allergy to the salivary fluid injected by the insect during the course of feeding. Data on the specificity of the reaction are accumulating. Although it is not possible to predict the degree of cross-reaction which may occur to salivary fluids of different species, it is usual to note distinct differences when different genera of biting insects are involved. More case histories, preferably beginning at a very early age, are required to define the usual patterns which develop in time in response to insect bites. Methods of alleviating the reaction are required, since frequently it is impossible to avoid being bitten, and insect repellents are not the complete answer to this problem. Although some success in reducing delayed reactions by means of injections of crude insect extracts appears to have been made on occasion, improvements in the extract are needed as a first step in seeking better ways of desensitizing patients suffering from insect bite reactions.

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PAPULAR URTICARIA

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Papular urticaria is one of the commonest and most troublesome skin diseases of early childhood. The controversy as to whether the eruption is of parasitic origin or whether it is related to digestive disturbances, allergic or otherwise, is now approaching its centenary, but is still vigorously debated. Since critical and impartial evaluation of the facts now available would seem to allow only one conclusion to be drawn, the literature is here examined in the hope that as a result some children may be spared misguided and meaningless dietary restrictions.

CLINICAL DESCRIPTION

Thomas Bateman[4] in 1813 wrote:

> There is scarcely any limit to the varieties of these papular affections, but I have observed one form which is so uniform in its character as to be entitled to notice here. It might be called lichen urticatus: its first appearance is in irregular inflamed wheals, so closely resembling the spots excited by the bites of bugs or gnats as almost to deceive the observer. The inflammation, however, subsides in a day or two leaving small, elevated, itching papules. While the first wheals are thus terminating new ones continue to appear in succession until the whole body and limbs are spotted with papules which become here and there confluent in small patches. The eruption is peculiar to children: it commences in some cases soon after birth and sometimes later and continues with great obstinacy for many months. Both the wheals and the papules are accompanied by intense itching, which is exceedingly severe in the night, occasioning an almost total interruption of sleep and a considerable loss of flesh.

Although later observers have added to our knowledge of the natural history of the condition, this clinical description is still among the best available.

Willan and his pupil Bateman made an effort to place the morphological description of skin lesions on a sound basis, but for the greater part of the nineteenth century the nomenclature of the papular eruptions of infancy and childhood remained confused. The same condi-

tion is often described under several different terms, and the same term has been applied by various authors to apparently different conditions. By the end of the century greater uniformity of nomenclature had been achieved, and the terms still used by most British and American writers, 'papular urticaria' and 'lichen urticatus,' were regarded as synonyms. Strophulus also is now generally regarded as synonymous with papular urticaria, but even this name has been used for other papular eruptions. In France strophulus and acute simple prurigo of Brocq are the terms in common use.

Jonathan Hutchinson[26] emphasized the greatly increased frequency of papular urticaria in the summer months. Of 109 cases, 82 were seen between May and October, 27 between November and April. Adamson[1] also noted that the peak incidence was between July and September. He found the sites most frequently affected to be the lumbar region, the buttocks, the outer sides of the arms and thighs and the wrists and hands. The papules succeeding the wheals are often surmounted by small vesicles, and occasionally bullous lesions develop. Adamson noted the greater rarity of the severe forms in his better-class patients. He gives the duration of the condition as a few days to two or three years.

Barber[3] in an excellent clinical description emphasizes the tendency, which other authors had previously noted, for the lesions to appear in groups of 6 to 20 papules at intervals of 2 or 3 days. Tomkinson,[41] reporting on 102 cases seen in Glasgow, merely confirmed earlier observations and noted that the sex incidence was equal.

Hallam[21] published a careful study of 52 cases. The minimum age at onset was three weeks and the maximum three years, the average age at onset being just under one year. The eldest patient was aged 13 and had had the condition since the age of one. Thirty-nine began in the summer months, but 21 of these also had the eruption at times during the winter. The sites most favoured by the eruption were the buttocks, the lower third of the back, the thighs, ankles and forearms. In only two instances were two cases present in the same family. Thirty-one hospital admissions all resulted in rapid fading of the eruption, and no new lesions developed while the children were in hospital. The onset of the eruption in four cases coincided with removal to a new residence. One child was twice cleared of the eruption while on holiday. Corson, Perlman, Waltz and Ash,[13] investigating 31 cases in Philadelphia, confirmed in general the work of other writers, but did not agree in considering involvement of the face to be uncommon.

Hallam[22] published further clinical investigations. Eleven children were admitted to hospital for the nights only, spending the day at home. In eight no new lesions developed, and in three cases a few sporadic papules appeared. Keeping the children in hospital by day

only had no beneficial effect. Bringing the bedding from home to hospital led to the appearance of a few papules in one case on one occasion only. Hallam collected the incidence figures for papular urticaria in children under 14 in eight dermatological out-patient departments in London and provincial hospitals for the years 1927 to 1930. The figures ranged from 0.8 per cent to 24 per cent of out-patient attendances, the 3 London hospitals showing a notably high incidence. The annual incidence often showed striking variation from year to year, and in all the hospitals the incidence was exceptionally high in 1930.

Among Gordon's[18] 50 cases more than one member of the family was affected in 6 instances. Onset or recurrence of the condition was noted on the patients' returning home from hospital in 10 cases. Kinnear[27] recorded the development of papular urticaria in 14 children aged 7 months to 9 years on arriving in this country from America. He confirmed that the eruption disappears when the child is admitted to hospital.

Pillsbury and Sternberg[32] investigated 60 cases. They found that 80 per cent developed below the age of 3. The sites involved, in order of frequency, were extensor forearms, the anterior surface of the upper arms and the back. Bray's[10] observations on 200 cases agree in general, but Bray considered that the face and other exposed parts were rarely involved.

Rook and Frain-Bell[34] studied 100 consecutive cases in an industrial area of South Wales. The sexes were equally affected. The minimum age at onset was 2 weeks and the maximum 7 years; the average age of onset was 1 year and 10 months, 89 per cent of the patients being under 3. Reliable information regarding seasonal incidence was available in 61 cases. Of these, 62.3 per cent were affected more severely in the summer and 9.2 per cent in the winter. The remaining 29.5 per cent were equally affected throughout the year. The distribution of the lesions was accurately recorded in 75 cases. In the majority the legs and lower trunk were principally involved. The face was involved in 5.8 per cent. In 31.7 per cent of the 85 cases in which special enquiry on this point was made, another member of the family was similarly affected. Since 21 per cent of these cases were in only children, in approximately 50 per cent of the families in which there were other children at risk, one or more of them had been affected. In many families the children were affected in succession rather than simultaneously, and frequently older siblings were stated to have suffered from "heat bumps" at about the same age as the patient. In other families the children were affected simultaneously. In all cases the characteristic irregular grouping of the papules was noted, and in several the lesions were grouped above or below the sites of pressure of elastic or other constrictions of underclothing, the actual site of constriction being

free. The eruption was sometimes profuse and involved the greater part of the trunk and limbs, conforming precisely with the classic conception of severe papular urticaria. In a few cases only one or two groups of papules were present and the diagnosis of insect bites would have been accepted without question by any observer. Often a circumscribed and a profuse eruption were seen in different members of a family at the same time or in the same child at different times. The lesions consistently disappeared when the child was admitted to hospital.

AETIOLOGY

The many aetiological hypotheses which have at one time or another found supporters can conveniently be considered under four main headings.

Digestive Disturbances and Food Allergy

Many of the earlier writers on papular urticaria attempted to relate the condition to digestive disturbances of various types and to dentition. As the concept of allergy developed during the first two decades of the present century the older theories were reclothed in new jargon, and many investigations were undertaken utilizing new technical procedures.

Radcliffe Crocker[14] believed that 'irritation of the alimentary canal' played an important role, but Adamson[1] was not satisfied with the current theory that digestive disturbances were responsible.

The authors who consider food allergy to be the cause of papular urticaria base their beliefs either on the results of skin testing or on the improvement of the condition on suppressing the foods considered to be responsible. Sidlick and Knowles,[37] using intradermal tests, found that 9 of 12 children with papular urticaria reacted to one or more proteins. Three were cured when the incriminated foods were suppressed, four were improved, and two were unimproved. This investigation was uncontrolled, and it is not stated whether any of the children was admitted to hospital and, if so, whether readministration of the food in hospital reproduced the eruption. Corson et al.[13] studied 31 cases and noted that the parents of the children were eager to incriminate foods in 23 cases. All skin tests were negative in 21 of the patients. In only one did elimination and readministration of a food substance apparently influence the eruption.

Walzer and Grolnick[43] in a similar investigation found positive skin tests to one or more allergens in only 9 of 36 cases of papular urticaria.

Specific therapy as suggested by the skin tests was of no value. These authors consider papular urticaria to be an atopic disorder.

Neither Hallam[21] nor Gordon[18] was able to establish a dietary factor in any of their patients.

Pillsbury and Sternberg[32] considered that the evidence in support of an allergic origin of papular urticaria was meagre. Bray,[10] however, strongly supported the relation to food allergy. He considered that fats, especially pig products, fish, eggs and chocolate were frequently responsible, and he claimed to have produced new lesions within 24 hours of feeding a child with pork, ham or bacon, and suggested that the coexistence of a thermal factor was necessary to produce the skin lesions, and attempted to explain in this way the seasonal incidence and the frequent development of new lesions at night.

Tate[39] investigated very thoroughly a series of cases of papular urticaria and gave a valuable review of the literature. He was unable to establish food sensitivity as a cause in any single case. He confirmed the observations of Hallam and others that the aetiological agent was connected with the patient's home environment and that it was not bedding or clothing, although it could be carried on these articles. The incidence of a family history of atopic disorders was no higher in his cases than in normal controls.

Urbach[42] claimed that sensitivity to a food protein or occasionally a carbohydrate substance could be established as a cause of the eruption in 28 per cent of his 225 cases.

Although food allergy is still widely accepted as a cause of papular urticaria, it is impressive that there is no published series of cases that we can discover, with the possible exception of Urbach's, in which it has been claimed that administration of any food to a child in hospital under controlled conditions has ever provoked papular urticaria. Many of those who have investigated the problem most thoroughly have been able to convince themselves that food sensitivity plays no part whatever in this disease. The seasonal incidence, the striking variation in frequency from year to year and the complete immunity of the child in hospital cannot be accounted for on the basis of food allergy.

Nervous Factors

Gordon[18] was impressed by the importance of psychological factors. Other authors have also raised this question, but it has received little consideration in recent years. Winnicott[44] considered that papular urticaria was a normal phenomenon of an erectile organ, a reaction to nervous stress or to external causes. Nervous stress can apparently heighten the reactivity of the skin, but there is as yet no evidence that nervous factors play any part in papular urticaria.

Infection

Botter[8] prepared a Seitz filtrate of the nasopharyngeal washings of four mothers whose children had papular urticaria. He dropped the filtrate into the nasopharynx of eight children who had recovered from papular urticaria and of one child with eczema. All the children had an eruption 'resembling papular urticaria although the efflorescences were somewhat smaller, sometimes grouped and not as intensely itching as in the typical disease.' No virus could be demonstrated. This work obviously requires confirmation. If an infective agent is responsible for papular urticaria, it is difficult to account for the complete lack of reports of contact cases when these children are admitted to hospital.

Parasites

Hutchinson[26] wrote:

> Is it not very singular that one author after another who has looked carefully at the spots has been puzzled to tell whether they were bites or not . . . My belief is that in very many cases the eruption is simply the result of flea bites on a pruriginous skin . . . It is the fact that only in a few persons does the flea bite cause a wheal which misleads the nurse.

Radcliffe Crocker[14] wrote:

> Hutchinson considers this disease to be entirely due to flea and bug bites and the like in the first instance. I am convinced this is far too narrow a view and that, though true in many cases, among the poor especially, irritation of the alimentary canal plays quite as, or even more, important a role in children than in adults, to say nothing of the recognized causes of urticaria.

The main objections raised to the parasitic origin of papular urticaria have been the relative infrequency with which more than one member of a family has been affected in most series of cases, the fact that new lesions did not develop when children slept in their own clothing and bedding in hospital (Hallam), and the apparent improbability of a parasitic origin in certain cases. Chipman[12] was convinced that fleas were responsible for papular urticaria, but in general the parasitic theory had few supporters during the first three decades of this century. Many authors have insisted on their own ability to differentiate insect bites from 'true papular urticaria,' but Templeton[40] was shown in Vienna cases labelled with this diagnosis, but which he had no difficulty in recognizing as flea bites. Lunsford[28] pointed out that the photographs of papular urticaria in some standard textbooks are highly suggestive of insect bites.

The evidence in support of the parasitic theory may be summarized under five headings: (*a*) clinical, (*b*) histopathological, (*c*) immunological, (*d*) epidemiological, (*e*) therapeutic.

CLINICAL. The papular lesion is essentially different from that of true urticaria, as Tate[39] was one of the first to emphasize. A patient of his with papular urticaria had a true urticaria due to fish, the lesions consisting only of evanescent wheals. Histamine phosphate, 1:1000, pricked into the skin of a child with papular urticaria produced only a transitory wheal as in normal controls. The biphasic course of the lesion of papular urticaria, a wheal followed by a papule, conforms exactly with the known reaction to insect bites as established by Mellanby.[30] The distribution of the lesions of papular urticaria, often asymmetrical, and grouped in irregular clusters, coincides with the observed pattern of insect bites and is not reproduced by reactions to inhaled or ingested allergens.

HISTOPATHOLOGICAL. The histopathological changes in papular urticaria were compared with those of known insect bites and of the reactions to the intracutaneous injections of insect allergens in patients with papular urticaria by Shaffer, Jacobson and Beerman.[35] All were essentially similar, and showed a moderate to heavy infiltration of lymphocytes with many eosinophils around vessels and epidermal appendages in the middle and lower dermis. Oedema and vasodilatation were also present in all cases, and focal necrobiosis of collagen was an occasional finding.

IMMUNOLOGICAL. The simple and practical survey carried out by Hamburger and Dietrich[23] in Vienna can be regarded as the first immunological investigation of the association between parasites and papular urticaria. They found that most children were not sensitive to bed-bug (Cimex) bites, but that about a third developed a wheal and later a bulla if exposed to the bite. Of children with papular urticaria, however, between 66 and 75 per cent were sensitive to bed-bug bites. The evolution of the bites was similar to the lesions of papular urticaria. Dietrich[15] showed that two-thirds of 50 children with papular urticaria were sensitive to bed-bug bites and the remainder to flea-bites. Every child was sensitive to one or the other, and some were sensitive to both. A more recent investigation[5] in the United States has given similar results. Thirty children with papular urticaria were tested with flea antigen and bed-bug antigen. Seventy-seven per cent were sensitive to one or both, whereas only 2 of 124 controls were sensitive.

Meanwhile more fundamental studies were establishing the pattern and the mechanisms of the responses of the human skin to the bites of arthropods. Mellanby,[30] working with the yellow-fever mosquito, was able to show that subjects bitten for the first time have an early erythematous macule followed by a delayed papule. Later the delayed reaction ceases to appear and there is less irritation. Eventually, after a period varying considerably from one person to another, complete desensitization is achieved and even the immediate reaction fails to

appear. Numerous observations and experiments[2, 17, 19, 24, 28, 31, 33] have confirmed and expanded Mellanby's work and have greatly extended its scope and application. Some arthropods, notably bees and wasps, inject directly injurious and toxic substances causing pain and discomfort which overwhelm the usually less dramatic efforts provoked by the normally non-injurious substances injected simultaneously. Other arthropods, including the mosquitoes, fleas, sand-flies and bed-bugs, inject only these latter substances, which are not injurious except to the previously sensitized host. The first and often many subsequent exposures provoke no detectable reaction. Eventually in most, but not all, persons sensitization develops and each bite provokes the formation of a firm papule after 24 to 48 hours. With continued exposure an immediate wheal precedes the papule. Finally desensitization is produced, first the papule and then the wheal failing to develop. Most biting arthropods probably inject more than one antigenic substance, and although human sensitivity may be limited to a single species, it may extend to related species or even to related genera.

We have summarised only that section of the large literature on this subject which is most obviously and directly applicable to papular urticaria. All aspects of the immunology of insect bites are more fully discussed by McKiel and West[29] (see p. 795). To recapitulate: The course of experimental arthropod sensitivities exactly parallels that of spontaneous papular urticaria. The age at onset, the variation in individual susceptibility, the customary spontaneous cure and the occasional persistence of sensitivity into adult life, are all accounted for.

Epidemiological. Many authors have noted that papular urticaria is more common and more severe in the poorest sections of the community and in the warm weather. Many have noted that a change of domicile often effects a temporary cure and that admission to hospital invariably does so. Although these facts are readily explained if the parasitic origin of papular urticaria be accepted, the protagonists of the parasitic theory have demanded more than circumstantial evidence, and some have attempted to demonstrate actual or presumptive contact with biting arthropods. Blank et al.[5] found known exposure to fleas in 26 of 87 cases and to bed-bugs in 8 and possible exposure in 72. Rook and Frain-Bell,[34] after careful study of the life histories of the cat- and dog-flea and the bed-bug, came to the conclusion that it was very seldom possible completely to exclude exposure to one or other of them. There were pets (cats or dogs) in the homes of over 80 per cent of the children, and many parents mentioned that neighbours' pets were frequently in the home. In many cases, the histories of some of which were summarised, the papular urticaria first developed shortly after the arrival in the home of a new pet. Bed-bug infestation was at that time still relatively common on old urban premises in South Wales. The

authors considered that only when a child was in hospital could exposure to parasites be excluded with absolute certainty.

An important step forward was taken by Bolam and Burtt,[7] the former a dermatologist, the latter an entomologist. They visited the houses of 30 children with papular urticaria and carried out an exhaustive inspection, collecting samples of dust from sites which the entomologist's knowledge suggested to be appropriate. Chicken runs, pigeon lofts and birds' nests under house-eaves were inspected and sampled, and occasionally the houses of relatives or neighbours often visited by the patient were also examined. Various species of flea were found in 21 of the 30 houses. The authors consider that even their conscientious search did not exclude a parasitic origin for the remaining nine cases. A localised flea infestation is easily overlooked, and in old property fleas can make their way through a party-wall from neighbouring premises, which it was not always possible to inspect.

THERAPEUTIC. Several attempts have been made to utilize parasiticidal agents therapeutically in papular urticaria. Blank and his colleagues[5] treated 54 cases with 5 per cent D.D.T. in talc as a dusting powder, and sprayed the patients' houses with "Flit" containing 5 per cent D.D.T. Eighty-six per cent were cured in two to three weeks. Of 88 cases treated by conventional methods, only 21 per cent were cured in an average of 10 weeks. Wulf and Holtschmidt[45] treated 80 cases of papular urticaria with a D.D.T. preparation; 69 were cured in 3 to 7 days without changes in diet or environment. The 11 remaining cases were cured within 14 days, but required simultaneous treatment for a secondary pyoderma. Rook and Frain-Bell[34] found it most difficult to assess the results of treatment with 5 per cent D.D.T. in talc. The patients were widely scattered over a large area and could not be visited. There was therefore no means of ensuring that the treatment was carried out. Nevertheless in many cases the simple application of the dusting-powder to child or pets produced a dramatic cure. Bolam and Burtt[7] found that disinfestation of pets and home cleared and kept clear 14 of their 21 patients in whose environment fleas had been discovered.

CONCLUSIONS. We consider with others who have investigated this disease[5,7, 36, 45] that the evidence incriminating the bites of parasites in specifically sensitized subjects as the cause of papular urticaria is now entirely convincing. There is no feature of the disease, clinical, histopathological, immunological or epidemiological, which is not fully accounted for by a parasitic origin. No alternative theory among the many which have been proposed can be retained if all aspects of the natural history of the disease are given due consideration. The apparent weak links in the evidence in favour of a parasitic origin are the occasional difficulty experienced in tracing a possible source of infestation,

and the not completely successful response to parasiticidal measures. For the entomologist these objections cannot be sustained: biting arthropods are very numerous, and some are difficult to find. The efficiency of any measures of disinfestation cannot, except by chance, be greater than the operator's knowledge of the life-history and habits of the parasite concerned. It is possible that there are causes of papular urticaria other than the bites of parasites, but they have not yet been demonstrated.

PARASITES INCRIMINATED. Most investigators[5, 12, 15, 23, 34] have, until recently, incriminated on circumstantial evidence or on the results of skin tests, the cat or dog flea, the human flea or the bed bug. Bowen[9] by skin tests incriminated mosquitoes in 24 cases and chiggers in 3. Rockwell and Johnson[33] noted that two of their patients with mosquito bites had been diagnosed by dermatologists as having papular urticaria. Fuchs[16] was able to show that *Scleroderma domestica* was responsible for a papular eruption in several members of a family and suggested that it might prove to be the cause of some cases of papular urticaria. 'Rather typical papular urticaria' was one of several patterns of eruption which Haggard[20] traced to rat-mites. Bolam and Burtt[7] and Bolam[6] had the advantage of expert entomological knowledge. They were able to incriminate fleas of five species, the cat flea being by far the most frequent offender. In one case the dog-louse was suspected.

It is clear that the clinical picture of papular urticaria can be produced by many different parasites. Geographical factors, the human environment, and the season will determine the species to which any person is exposed. Table 14 lists those species proved to be responsible for, or strongly suspected of causing, papular urticaria. No doubt many additions will be made.

Since various species of flea and the bed bug have most often been held responsible for papular urticaria, their life histories will be briefly considered.[11, 25, 38] The eggs of the fleas concerned are laid in the nests

TABLE 14. *Species of Parasites Responsible for Papular Urticaria*

SPECIES	ENGLISH NAMES
Ctenocephalides canis[15,28]	Dog flea
Ctenocephalides felis[5,6,34]	Cat flea
Ceratophyllus gallinae[6,7]	Hen flea
Ceratophyllus farreni[6,7]	House-martin flea
Ceratophyllus columbae[6,7]	Pigeon flea
Pulex irritans[5,7,15,28]	Human flea
Cimex lenticularis[5,15,34]	Bed bug
Scleroderma domestica[16]	
Liponyssus bacoti[20]	Rat mite
	Dog louse[6]
Anopheles species[9]	
Aedes species[33]	Mosquitoes

or sleeping quarters of their hosts. They are dry and do not remain attached to their hosts' hairs or feathers. Eggs are usually laid in warm weather, particularly when the humidity is high, and the incubation period, which varies from 2 to 12 days, is shortest under these optimum conditions. The larval stage lasts from 9 to over 200 days, depending on whether conditions are favourable. The larvae can be found in the crevices of floors, under carpets, in kennels or in chicken runs. They can survive with little or no food. The length of the pupal period also varies with the temperature and is between 7 and 300 days. The adult fleas visit the host only for short periods for feeding and can remain for many months without food. The host specificity of fleas is low. The maximum prevalence of fleas during the warm moist months of the year coincides with the maximum incidence of papular urticaria.

The bed bug, *Cimex lenticularis*, lays its eggs on rough surfaces, in cracks and crevices and behind woodwork or wallpaper. The eggs are attached by a quick-drying cement and may therefore require stiff brushing to remove them. In warm weather the adult may lay two or three eggs daily, but in spring and autumn, when the temperature is lower, the frequency of egg laying is considerably reduced. The eggs do not survive longer than three months in uninhabited houses. After hatching, the nymph can live for three or four months at low temperatures without food, but further development cannot occur. If food is available, the nymph moults five times before reaching full adult development. An average time of 10 weeks is required from egg to adult.

The adult bed bug is a flat, oval insect ⅛ inch long and ⅛ inch broad. Its colour may be light or dark brown, but after feeding is usually purple or red. It is chiefly nocturnal, but will feed in the daytime if conditions are favourable, and is said to be most active just before dawn. Under ideal conditions of temperature, feeding takes place about once a week, but in colder weather the frequency is reduced. The time required for feeding varies from 5 to 12 minutes, after which the insect leaves its victim as fast as possible. The adult bed bug has been known to survive a year without feeding and for as long as four years with occasional feeds. The temperature of the house is likely to have a considerable effect on the breeding of the bugs. If the temperature never falls below 55° F. for more than a few hours during the winter as, for example, in a bed-sitting room, feeding and breeding will continue throughout the year. If the room is without artificial heat, breeding will cease and feeding will become very infrequent during the winter. The bed bug is capable of travelling long distances in search of food, even from one house to another. The temporary storage of furniture or its carriage in an infected van are all potential sources of infestation. The percentage of houses infested with bed bugs is highest

in large cities, and despite the efficacy of modern methods of control, bed-bug infestation is still common.

The life histories of the parasites less often incriminated may be sought in the textbooks mentioned or in any good text of applied entomology.

DIAGNOSIS

The clinical features are so distinctive that few diagnostic problems arise unless gross secondary infection has resulted from scratching. The firm papules, on the trunk and limbs and sometimes on the face, often in clusters and developing in crops at irregular intervals and often followed by pigmented macules, must be distinguished from the wheals of true urticaria, evanescent and usually symmetrical (Figs. 38, 39, 40). The eruption of scabies favours the genitalia and the axillae, the papules are smaller, and the diagnostic burrows are present on hands, wrists, axillary folds and penis, and, in infants, the soles.

Once the morphological diagnosis has been established, the causal parasite must be sought. A detailed chronological history of the course of the eruption in relation to the child's activities, including visits to friends and neighbours, may provide suggestive information. Enquiry also must be made concerning living conditions and pets: inspection of the house along the lines suggested by Bolam and Burtt[7] may result

Fig. 38. Clusters of excoriated papules and vesicles on the lower extremities of an infant. Hyperpigmentation at sites of subsiding papules is noticeable. (Illustrations courtesy of The Skin and Cancer Hospital Unit, Department of Dermatology, Temple University Medical Center.)

Fig. 39. Tension vesicle and excoriated older papules on the arm of a 5-year-old Negro child.

Fig. 40. Clusters of asymmetric papules in various stages of development with localisation on the extremities and along the belt area.

in the actual discovery of the parasite. Most often circumstantial evidence alone is available for evaluation. Specific antigens for skin-testing are not always readily available, but can be of considerable assistance in diagnosis (Fig. 41). A negative intradermal test completely exonerates the suspected parasite. A positive reaction confirms the existence of specific sensitivity, and although it does not provide conclusive evidence

Fig 41. Positive wheal reaction to a water-soluble flea extract in a child with papular urticaria. Tests to other biting insects were negative.

that the parasite is responsible for the present eruption, it adds weight to the epidemiological evidence.

TREATMENT

Disinfestation

The efficacy of any measures adopted must obviously depend on the reliability with which the source of the infestation has been determined. Nevertheless the empirical use of a disinfestation routine can sometimes produce dramatic results even when the source of infestation is not apparent from the history. The natural history of the pest must always be carefully considered. We have known the unnecessary destruction of a pet without disinfestation of its sleeping quarters to be followed by an increase in the severity of the fleas' attacks on the child, after the removal of their natural host. The following measures are simple and practical.

Fleas. Treat the animals' sleeping quarters with a 5 per cent D.D.T. spray in kerosene, paying special attention to bedding, floor coverings and crevices. Dust dogs with 5 per cent D.D.T. powder. For cats 'rotenone' or pyrethrum powder is to be preferred, since cats may lick their fur and D.D.T. may prove toxic.

Bed Bugs. Treat floor coverings, floor boards, skirting and furniture with 5 per cent D.D.T. in kerosene. Residual toxicity is said to persist for nearly 200 days.

Symptomatic Treatment

In the majority of cases if disinfestation is carried out promptly and efficiently, calamine lotion and simple sedation with phenobarbitone (phenobarbital, U.S.A.) for a few nights are all that is required. We have not found the antihistamines effective. Where bullous lesions have become secondarily infected antibiotics may be indicated systemically or locally. Occasionally when the eruption is exceptionally profuse and of long duration, the child may have lost weight as a result of lack of sleep and perhaps unnecessary dietary restrictions. In these cases admission to hospital for a few days may be desirable, since it not only establishes the parasitic origin of the eruption beyond doubt, but also allows time for thorough disinfestation before the child returns home.

D.D.T. 10 per cent in talc may be used as a dusting powder. It has proved particularly useful as a preliminary measure to be employed whilst the source of the parasites is sought and thorough disinfestation planned. Eurax ointment, combining parasiticidal and antipruritic properties, has also been found useful.

It occasionally happens in cases in which there is strong circumstantial evidence incriminating flea or bed-bug bites that disinfestation is difficult to carry out effectively or is even impracticable for economic or social reasons. In other instances, as when sensitivity to mosquitoes is concerned, complete avoidance of exposure may be impossible. In such cases desensitization deserves consideration. We have had no personal experience of it. The subject is fully covered in the article by McKiel and West (p. 795).

SUMMARY

The clinical features and natural history of papular urticaria are described.

The aetiological theories which have recently found exponents are reviewed.

The evidence in favour of the parasitic theory is discussed in detail. The substantial support which this theory receives on clinical, histopathological, immunological and therapeutic grounds is considered fully to justify the conclusion that papular urticaria is a pattern of reaction of the specifically sensitized skin to the bites of certain parasites. The parasites so far incriminated are listed, and the life histories of the more important are summarised.

Differential diagnosis from true urticaria and from scabies is seldom difficult.

The planning of disinfestation and the treatment of the individual patient are briefly outlined.

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DIAPER DERMATITIS

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Although Parrot[13] is credited with having described an affection of the skin localized to the diaper area in 1877, it seems reasonable to assume that a covering to catch the drippings of the socially inept infant antedated this observation. Parrot pointed out the constant localization of the dermatitis to the thighs and to the gluteal, perianal and genital areas, and also described both vesicular and papular forms. The vesicular form he called the "erythema of athrepsia" because it was associated with vomiting and cachexia in the first few days of life. He attributed more significance to the papular erythema, for he thought that it was of syphilitic origin and suggested that it be called lenticular syphilis. This idea of the importance of syphilis in the production of diaper dermatitis persisted for years in spite of Jacquet, Hallopeau and Sevestre's objections that the eruption had nothing to do with syphilis, but was only a morphologic variant of the vesicular erythema.[11]

In 1888 Jacquet[9] described a series of morphologic changes associated with the eruption. An erythematous dermatitis (*erytheme simple*) was described which was localized to the genital area, the upper portions of the thighs, calves, sacral area, and the abdomen up to the umbilicus. The dermatitis spared the creases in the genital-crural region. In some instances large serum-filled blisters, which resembled a second-degree burn, appeared in the involved areas; these healed without scarring. At times superficial erosions and ulcerations localized particularly to areas of pressure, i.e. the heel, ischial tuberosities, malleoli. Later, Friedjung and Bokay[2] described similar ulcerations on the glans penis in circumcised male infants.

Jacquet also described a vesicular and papular form of diaper eruption in which lesions were seen predominantly on the proximal lateral aspects of the thighs, buttocks, scrotum, labia, penis and the flexural surfaces of the upper thighs and calves. Because of mechanical irritation and maceration, small purplish-red patches appeared (*erytheme vesiculeux erosif*). In some instances, because of continued irritation, the papules became nodular with an inflammatory infiltrate which resembled a syphilitic papule (*syphiloide erytheme papuleux posterosif*). He pointed out the predilection of these lesions for the buttocks and their absence from the anal cleft, as would be the case with syphilis.

Having clarified the different types of skin reaction in the diaper area as morphologic variants of the same process, clinicians were still concerned about the differentiation from syphilis. In 1908 in a study on the histopathology of diaper dermatitis, Ferrand[7] expressed the diagnostic apprehension of the clinicians of the day as follows: "In the presence of an eruption which looks so much like syphilis, the diagnosis must rest in suspense until one is driven as a last resource to a biopsy which allows one to histologically examine a small piece of tissue and to search for treponemes in the section."

Although there was unanimity of opinion about the role of syphilis in differential diagnosis, opinions about the causation of the dermatitis were varied. Theories on the etiology were well summarized in 1930 by Leiner.[11] Sabouraud and Brocq believed that the dermatitis was microbial in origin. Juliusberg's demonstration of several forms of gram-negative bacteria in the epidermis of a histologic specimen from an infant with syphiloide posterosif (Jacquet) at the German Natural History Congress in Cologne in 1899 reinforced this impression.

Yeast organisms were found on the eczematous surface and in the vesicles by Bohn, Valleix and Ibrahim. Marfan[12] felt that the yeast intertrigos could be differentiated from the gluteal erythemas by their characteristic morphologic appearance.

Parrot first called attention to the role of nutrition in the production of the dermatitis when he noted the vesicular form occurring in cachectic newborn infants. But Jacquet, Sevestre and Hodara observed the vesicular form in normal infants several months old. The known difference in pH of feces of breast- and bottle-fed infants led to further investigation of the role this played in development of diaper dermatitis.

There are distinct differences in the intestinal flora and the reaction of the feces of infants fed with human milk as compared to those infants fed cow's milk. Stools of the normal breast-fed infant are acid, whereas the pH of the feces of infants fed cow's milk usually falls within the neutral or slightly alkaline range. Intestinal flora of healthy breast-fed infants is characterized by the prevalence of *Lacto-*

bacillus bifidus, whereas the cow's milk formula is associated with a mixed intestinal flora. Although it was originally felt that the perianal dermatitis seen during the newborn period was related to an alkaline pH of the feces in the formula-fed infant,[13] Tanino's comprehensive study refutes this thesis as a major factor in the genesis of diaper dermatitis.[16]

Kreutzer was of the opinion that the principal cause of the dermatitis was alkaline urine, which could be produced experimentally by feeding food resulting in an alkaline reaction of the urine.

Ferrand's[7] experimental efforts to reproduce the dermatitis by placing compresses of feces and urine on the skin of antecubital fossae of children with gluteal erythema failed. Most observers at the turn of the century, however, believed that the dermatitis in the diaper area was produced by mechanical or chemical irritation caused by contact with feces or urine, or both, and that either bacterial or yeast infection was coincidental.

Zahorsky[17] tried to correlate the almost constant association of ammonia in the diaper with the ammoniacal dermatitis in affected infants. Although the association of the dermatitis with the odor of ammonia was well established in clinical practice, the origin of the ammonia was not determined until Cooke's[6] isolation of *Bacillus ammoniagenes* in 1921 and the demonstration of the role of this bacterium in the production of ammonia from urine. He showed a relation between dermatitis and ammonia and the isolation of *B. ammoniagenes* on cultures of swabs from the rectum. A constant relation between the presence of the saprophytic urease-producing bacillus in the stools and the ammoniacal diapers of the infant was shown. To further establish a cause-and-effect relation, the dermatitis was produced experimentally on the forearm of an adult by applying gauze compresses covered with rubber sheeting and a bandage for 16 hours on 2 successive days. In order to rule out the possibility that the organism itself produced a reaction, compresses with a broth culture of *Bacillus ammoniagenes* were used, as well as a 1 per cent urea solution, freshly contaminated with pure culture of the bacillus. No reaction was produced with the organism alone, but a typical erythematous dermatitis was produced with the combination of the bacillus and the urea solution. As the dermatitis regressed the typical changes of a primary irritant reaction were observed: the skin showed characteristic glistening with slight wrinkling and subsequent exfoliation. This explanation for the causation of the eruption has been widely accepted and has naturally been the basis of most treatment and prophylaxis of dermatitic reaction in the diaper area.

If the conclusions about the role of ammonia in the production of

diaper dermatitis were completely correct, the dermatitis should disappear with prophylactic measures and could be routinely cured with appropriate measures to combat the formation of ammonia. That this has not been the cause is suggested by reports of increased frequency of diaper dermatitis and an increased incidence of persistent diaper rash by Kessler[10] and Benson.[1]

On the assumption that the impressions of Kessler and Benson are correct, two factors must be considered. First, increased tendency to control the infant's incontinence by covering the diaper with an impervious cover increases the incidence of skin damage. Second, an attractive alternate hypothesis could be the almost universal abandonment of breast feeding, although the significance of the altered pH of the stools due to diet has been disproved.[15]

It is difficult to obtain information on actual incidence of diaper dermatitis, and false impressions of the increased incidence may be the result of the observation of severe persistent reactions. It is this type of dermatitis, which has resisted good pediatric management, that we have seen frequently in consultation. In these instances the routine therapeutic approach, based on the premise that ammonia is the cause of the dermatitis, has failed. The varied morphologic appearance and distribution of these eruptions emphasize the need for a

Fig. 42. Predisposing and activating factors in diaper dermatitis syndrome.

re-evaluation of the mechanisms responsible for the dermatitis. It is the purpose of this paper to discuss the multiple factors responsible for causation of the dermatitis and to suggest a classification based on distribution, morphology and histopathology, and to describe methods of treatment based on an analysis of possible etiologic factors.

It would seem most reasonable to call this the diaper dermatitis syndrome, from an analysis of the multiple factors which may lead to the production of dermatitic changes peculiar to this area. Those factors which are responsible for the dermatitis may be broadly classified as predisposing and activating factors (Fig. 42).

PREDISPOSING FACTORS

Predisposing factors are influences on the skin which may alter its response to irritation. These may be genetically inherited traits, as in the seborrheic diathesis and the reactive skin, or they may be due to an altered response of the cutaneous system due to systemic disease.

The Reactive Skin

It is recognized that some children inherit a kind of reactive skin from their parents which may be more easily irritated by contact with sensitizing preparations or irritants than the normal skin of others.

Seborrheic Diathesis

The seborrheic diathesis is an inborn physiologic trait which seems to be genetically transmitted. It has several distinct characteristics, including the distribution of the eruption, frequent association with an oily skin during adolescence and adult life, and vulnerability to secondary bacterial and yeast infection. In infancy the influence of this sort of inheritance is manifest in the diaper area.

Systemic Disease

A few systemic diseases are frequently associated with a persistent dermatitic reaction in the diaper area. Those diseases most frequently mistaken for persistent *ammoniacal* dermatitis are Letterer-Siwe disease, acrodermatitis chronica enteropathica, and syphilis.

ACTIVATING FACTORS

There are a number of activating factors which may initiate the der-

matitis in the predisposed infant. It is undoubtedly true that any of the factors to be mentioned as collaborators may produce dermatitis in the neglected child. We are particularly interested, however, in the influence of these activating factors in the production of dermatitis in the predisposed infant.

Maceration

The subtropical environment produced by continuous contact with the moist diaper results in water-logging of the skin. Damage produced by moisture is present in all infants in diapers and is probably one of the most important triggering factors in the predisposed skin. The macerating effect is increased by applying an impervious diaper cover, or two or three diapers at bedtime to prevent soaking of the bed.

Sweat Retention

Hyperkeratotic plugging of the poral orifices of the sweat ducts and sweat retention are the natural sequences following maceration and water-logging of the stratum corneum. Keratotic plugging of the sweat gland orifices can be demonstrated histologically after experimental production of maceration of the skin by continuous moist compresses. In the infant without predisposing factors the resultant irritation is minimal and rarely requires the physician's care, but in the infant with predisposing factors these changes may mark the beginning of "diaper dermatitis" (Fig. 43).

Fig. 43. Sweat retention syndrome showing erythematous papules and papulovesicular lesions in diaper-covered area.

Contactant Factors

Contactants may be divided into allergic and primary irritant types. The allergic contact type of dermatitis is the result of epidermal sensitization and may be produced after an initial contact and an incubation period followed by recontact. In contrast, a primary irritant type of reaction can be produced regularly in all patients at the time of first exposure.

Allergic Contactants. In a consideration of the multiple factors responsible for diaper dermatitis, allergic contactants play a relatively minor role. The infrequent occurrence of allergic reactions in spite of contact with potential allergens under circumstances of skin damage conducive to sensitization emphasizes the immunologic immaturity of the cutaneous system. Sensitization reactions are most frequently produced by the fluorochromes used in detergent soap preparations, rubber and plastic diaper covers.

Primary Irritants. Feces regularly produce a primary irritant effect on the skin. The role of feces can be rapidly seen in the infant who has frequent loose stools and a dermatitic reaction in the areas where contact with feces occurs. Unless the feces are removed immediately, dermatitis appears and rapidly proceeds to eczematization and erosions within as little time as four to six hours.

Some foods such as soy products have a tendency to cause increased numbers of bowel movements (Fig. 44). Ingestion of fresh fruits and some fresh vegetables (tomatoes) frequently produces a diarrheal tendency.

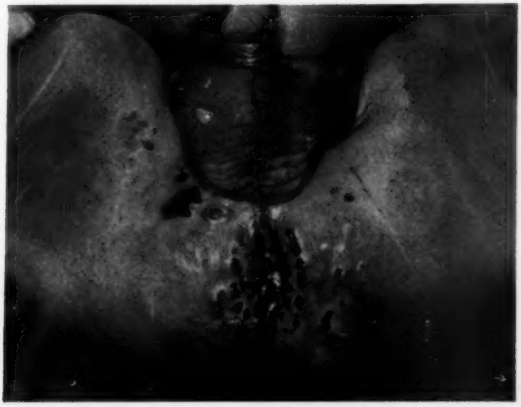

Fig. 44. Multiple erosions of the skin in the perianal area associated with frequent soft stools caused by soy bean milk substitute. (F. Swift in *Pediat. Clin. North America,* Vol. 3.)

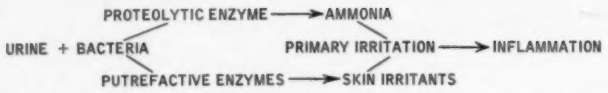

Fig. 45. Production of skin irritants from urine by proteolytic and putrefactive enzymes.

Freshly voided sterile urine will not produce any visible reaction on normal intact skin, but there is universal agreement as to the importance of old, bacterially contaminated urine in the production of dermatitis. If decomposing urine is analyzed for changes in odor and pH, at least two simultaneous breakdown products can be recognized, according to Rapp.[15] The one is associated with a foul to sour odor accompanied by little change in pH, and the other is associated with a rise in the pH and a characteristic odor of ammonia. Erythema may be produced by patch-testing normal skin with either alkaline ammoniacal urine or the foul- to sour-smelling neutral urine. In the foul-smelling urine a close correlation was shown to exist between the odor of the urine and its ability to produce erythema regardless of the pH.

From these data Rapp[15] concluded that there were at least two types of skin irritants produced in the urine by the action of proteolytic and putrefactive enzymes from the bacteria of the skin and feces (Fig. 45). In an experimental study of skin sensitivity of the gluteal skin of 3-month-old infants he used patch tests covered by plastic adhesive and showed that erythema production by a 1 per cent ammonia solution was pH-dependent and appeared only at a pH of 8 or above, while the erythema production by the putrefied ammonia-free urine was not pH-dependent. To further evaluate the significance of the 2 irritant factors, urine was incubated at 37° C. for 18 hours to permit the bacterially induced enzymatic changes to take place. The malodorous urine (ammonia and foul-smelling odor) was then autoclaved to destroy the ammonia odor, although the foul putrefactive odor remained. The pH of the solution was adjusted to 5 to 8 by adding dilute hydrochloric acid or dilute sodium hydroxide. Dermatitis developed in all instances under the patches in the absence of ammonia, irrespective of the pH of the urine.

In an experiment designed to test the dermatitis-preventing capabilities of specific inhibitors of the putrefactive enzyme and the ammonia-producing enzyme, patch test experiments were done using both inhibitory agents in one patch test experiment and only the ammonia-producing enzyme inhibitor in the other. In the presence of both enzyme inhibitors in the pad no ammonia or foul odor was detected and no skin irritation appeared at the test site. Dermatitis was produced in the experiments in which the putrefactive changes were allowed to develop and ammonia production was inhibited. From

these experiments Rapp concluded that two primary irritant factors are produced by the action of enzymatically catalyzed reactions on the urine.

Goneigenic Factors

Goneigenic causation is a term which has been coined to emphasize the association of emotional problems in the mother with production or persistence of a dermatitis in the diaper area. This mechanism may account for failure of the child to respond even in the presence of correct analysis of the etiologic factors. This factor may manifest itself in one of several ways: the mother does not carry out the instructions for treatment because she has a need for the child to have a dermatitis; she neglects the infant because she may be too involved with her own problems; she may produce additional irritation by being overassiduous in cleansing of the affected area. Instances in which gonieogenic factors are operative are not common, but do occur and should be evaluated in the presence of a refractory dermatitis.

Infection

In the order of the relative frequency with which they may be seen, yeast, bacterial or viral infections may be localized to the diaper area. The localization to this area is conditioned by the damage to the skin produced by constant moisture.

Fig. 46. Herpes simplex infection in diaper-covered area, showing evolution from vesicle to crusted lesion. The virus was isolated by chorioallantoic membrane inoculation. (Courtesy of J. A. Dudgeon, M.D., and Department of Medical Illustration, The Hospital for Sick Children, London, England.)

Yeast infection is generally regarded as an indication of maternal neglect despite the fact that severe infections may develop even when the standard of care is high. Bound[3] showed that yeast vaginitis was more often present in mothers of infants who had a yeast diaper dermatitis than in mothers of healthy infants, the incidence being 27 and 6 per cent respectively. Nevertheless oral thrush need not be present before making a diagnosis of yeast infection in the diaper region, for it is found in less than one third of the infants.

Bacterial infection may be either primary or secondary (see p. 751). Primary infections are usually produced by staphylococci and are usually of the vesiculo-bullous impetiginous type. In secondary pyoderma the usual hallmarks of pyogenic infection (purulent discharge, furuncles, cellulitis, systemic reaction) may be absent.

Viral infections in the diaper area are uncommon, but may be produced by vaccinia or herpes simplex viruses (Fig. 46). Vaccinial infection may follow vaccination in the presence of irritation of the skin in the diaper area or may result from accidental vaccination following the vaccination of a sibling for smallpox. Herpes infection of the skin is of the primary type and may be associated with a severe systemic reaction and regional lymphadenopathy. It may appear on the damaged skin shortly after the appearance of a recurrent herpes infection in a member of the family group who has had close contact with the infant.

Trauma

The role of mechanical irritation was originally emphasized by Jacquet in the localization of the dermatitis to the convex portion of the

Fig. 47. Contact dermatitis showing lesions predominantly on thighs at site of irritation by diaper in a toddler.

buttocks and other areas of pressure from the diaper. This is accentuated by too tight application of the diaper, particularly in the infant in whom ammonia is acting as a primary irritant (Fig. 47). Irritation and dermatitis from rubbing of the wet diaper on the medial aspects of the thighs are seen in the toddler.

MORPHOLOGIC VARIATIONS

The original observers attributed the different morphologic manifestations of diaper dermatitis to variations of a single process. This is true as far as it goes, but differences in morphology are also due to variation of the host's response and to different etiologic factors. As in the case of dermatitis involvement in other skin diseases, it is rare to have a pure form of dermatitis not complicated by secondary factors. This is particularly true in the diaper area, where maceration and sweat retention are necessarily accompanying etiologic factors in any dermatitic reaction. In spite of the multiple factors operating in the production of the dermatitis, sometimes the factor which initiates the problem produces a sufficiently characteristic distribution or morphology as to suggest the underlying cause.

Morphologic changes vary from diffuse erythema in which the skin has a parchment-like appearance, to nodular infiltrated lesions. Between these two extremes vesicles, pustules, bullae, eczematous reactions, and annular erythematous lesions simulating ringworm infection may be seen (Fig. 48). In some instances the dermatitic reaction in the diaper region may be so severe that it may be followed by a generalized, scaling patchy eruption or a papulovesicular dermatitis of the palms and soles (Figs. 49, 50).

Fig. 48. Infant with seborrheic diathesis and diaper dermatitis syndrome, showing annular erythematous lesions resembling ringworm.

Fig. 49. Infant with seborrheic diathesis and diaper dermatitis syndrome showing generalized papulosquamous eruption.

Fig. 50. Infant with severe diaper dermatitis syndrome, generalized dermatitis and vesicular eruption on palms and soles.

HISTOPATHOLOGY

Parrot[13] was the first to report the histopathologic changes associated with the dermatitis, but he described only the erythematous phase of the process. Hodara[8] called attention to the lack of histopathologic evaluation of the changes of the skin in the clinical studies of erythema gluteale by the French authors. (He reported a detailed microscopic evaluation of the morphologic variations seen clinically in two infants with erythema gluteale who had died.) By doing multiple biopsies and using different staining techniques, he studied the scaling erythematous lesions, erosions and ulcers. From careful studies of the changes in the epidermis, dermis and vessels he concluded that the only significant difference between the histologic changes in eczema and diaper dermatitis was the intracellular edema with destruction of the epithelial cells in diaper dermatitis and intercellular edema with vesicle formation in eczema. The changes in the dermis, consisting in dilatation of vessels, edema, and perivascular infiltrate, were indistinguishable.

Ferrand[7] extended the study of the histopathologic changes in diaper dermatitis and did serial biopsies showing the sequential changes in the skin during the evolution of the eruption. Although the microscopic description of the changes was identical with Hodara's, the interpretation of the findings was somewhat different. Ferrand felt that the vesicle formation was the result of the intercellular edema as in any eczematous process.

Fig. 51. Primary irritant contact dermatitis illustrating uninvolved skin in genitocrural areas.

In a recent study[4] of the histopathologic changes seen in the diaper dermatitis syndrome, the changes varied, depending on the etiology of the dermatitis. A dermatitic reaction as described by Hodara and Ferrand was seen characteristically with the contact type of dermatitis. The dermatitic response of the skin was not specific and was indistinguishable from other dermatitic reactions. Specific histologic changes may be seen in the diaper dermatitis syndrome, in syphilis, Letterer-Siwe disease, and viral, bacterial and yeast infections.

DISCUSSION

Variations in morphology and distribution, depending on the etiologic factors responsible for the dermatitis, are obvious to the experienced observer (Figs. 51, 52). An awareness of these clues can make them useful in differential evaluation of these factors and is essential for proper treatment.

Fig. 52. Primary irritant contact dermatitis showing variation of cutaneous response.

Fig. 53. Diaper dermatitis syndrome illustrating primary involvement of skin in genitocrural folds of an infant with seborrheic dermatitis.

In the infant who has inherited the *seborrheic diathesis* the dermatitis first appears in the genitocrural folds. As the dermatitis spreads, it involves the proximal aspects of the thighs, the pubic area and the anal cleft (Fig. 53). If it is not treated or is mistreated, the worsening dermatitic reaction is accompanied by patches in other intertriginous areas (axillary spaces, the folds of the neck, and the antecubital and occasionally the popliteal spaces). Yellowish scaling lesions indistinguishable from cradle cap appear on the scalp, and an erythematous scaly and weeping dermatitis appears in the retroauricular area. The cheeks are involved in the process, and in this location the dermatitis closely simulates atopic dermatitis (Fig. 54).

The skin response to *primary irritants* in urine and feces varies from an erythematous, shining, peeling exfoliation to bullae and infiltrated papules. In all instances of primary irritant contact dermatitis the

Fig. 54. Dermatitis on cheeks simulating atopic dermatitis accompanying diaper dermatitis syndrome. Face of child illustrated in (*A*) Figure 53, *A*; (*B*) Figure 53, *B*.

Fig. 55. Primary irritant contact dermatitis illustrating skin involvement at sites of most intimate contact with wet diapers.

skin in the intertriginous areas of the genitocrural fold and between the buttocks is clear (Fig. 55).

The localization of the allergic contact type of dermatitis is similar to primary irritant dermatitis, being limited to areas in close contact with the diaper, thus sparing intertriginous areas. The skin response varies from an erythematous scaling dermatitis to a vesicular eruption with pinhead-sized vesicles and edema of the involved skin (Fig. 56). The impregnations of the diaper by the fluorochrome dyes and the

Fig. 56. Allergic contact dermatitis caused by sensitization to ointment used to treat eroded hemangioma.

Fig. 57. Bacterial infection (staphylococcus) illustrating resemblance to primary herpetic infection.

detergents used for cleansing the diapers are probably the most frequent sensitizers.

Primary bacterial infections in the diaper area are usually of the superficial variety and resemble impetiginous pyodermas seen on other areas of the skin. Occasionally they may resemble a herpetic infection because of the spread of lesions on the damaged skin (Fig. 57). Direct microscopic examination of smears stained with Gram stain is useful in the diagnosis.

The history of chronic recalcitrant dermatitis not responding to local

Fig. 58. Diaper dermatitis syndrome caused by *Candida albicans*, illustrating satellite pustules and edema of penis and foreskin.

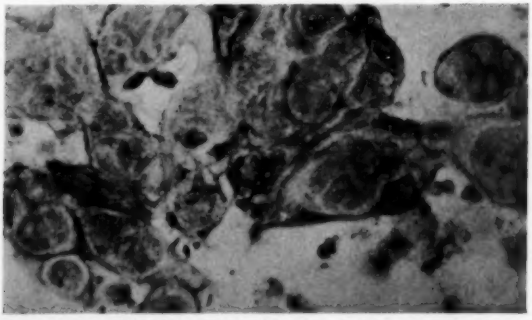

Fig. 59. Multinucleate epithelial giant cells seen in Giemsa-stained smear obtained from herpetic vesicle.

treatment with antibiotics and steroids is typical of a *yeast dermatitis*. The dermatitis usually involves the genital-crural fold and the anal cleft. Erythema and edema, particularly of the foreskin and scrotum in the male (Fig. 58), and satellite vesiculo-pustules at the border of the dermatitic reaction suggesting sweat retention or pyoderma are characteristic. Direct microscopic examination of the roof of one of the vesicles may reveal spores or mycelia, and a culture on a suitable nutrient medium will grow *Candida albicans*. A biopsy of one of the lesions will show the organisms in the keratinous layer if proper staining techniques are used.

Unlike other dermatitic reactions, *viral infections* are usually associated with a high temperature elevation, regional lymphadenopathy and malaise. Direct microscopic examination of cells obtained from the

Fig. 60. Persistent proliferative lesion on the labia of child with Letterer-Siwe disease.

Fig 61. Acrodermatitis chronica enteropathica illustrating erosive dermatitis in diaper, perioral and pressure areas.

base of fresh vesicles and a biopsy will give definite diagnostic information (Fig. 59).

In *spirochetal infection* the skin lesions are located primarily in the intertriginous regions between the buttocks and the genital area. The morphology of nonsyphilitic lesions in these areas may be confusing,

and when in doubt, a darkfield examination on material obtained from the lesions should be done. In addition, the infant's and mother's serologic tests for syphilis would be reactive.

In *Letterer-Siwe disease* persistent proliferative lesions may be present in the genital-crural or anal area in association with other changes on the skin which suggest an atypical seborrheic dermatitis (Fig. 60). A biopsy from a lesion will reveal the characteristic monomorphic histiocytic infiltrate.

In *acrodermatitis chronica enteropathica* the dermatitis in the diaper area is associated with perioral dermatitis, diarrhea and cachexia (Fig. 61).

TREATMENT

Prophylactic Treatment

For the most part the diaper dermatitis syndrome is a completely preventable reaction. If the various etiologic factors are taken into consideration, it is possible to outline a course of prophylaxis which will be uniformly successful.

Removal of impervious diaper covering and the wearing of one diaper are the first line of attack, since maceration and secondary sweat retention are the first consequences of continued moisture on the skin. In the first year of life there is a greater tendency toward sweat retention in some infants than in others, even when diaper covers are eliminated. The skin may be protected in such instances by the application of Lassar's paste with each diaper change. In an infant who has had recurrent dermatitis in the diaper area because of reactive skin or seborrheic diathesis, it seems reasonable to recommend that impervious diaper covers not be used except for brief periods when the child has to be socially acceptable. Mothers must be cautioned against using two or three diapers at night to sop up the moisture when diaper covers are not used, for this has the same macerating tendency as does an impervious diaper cover.

It had been demonstrated that urease and putrefactive enzymes produce primary irritants, and that treatment of the diaper may minimize this tendency. A quaternary ammonium compound combined with a putrefactive enzyme inhibitor in the diaper rinse completely fulfills the requirements for prevention of irritation from these causes.

Thorough cleansing of the skin after diaper changing is essential to remove bacteria and fecal contamination. In infants with particularly reactive skin it is worth while to use a soap substitute containing hexachlorophene. In these children it is also useful to use a protective paste, and for this we recommend Lassar's paste as being as effective as any other protectant on the market, and cheaper.

To prevent irritation the diapers should be changed promptly after a bowel movement, and frequently after voiding, although if a single diaper is used without a diaper cover, the majority of the urine dribbles through. Changing the bedding and diaper is essential in the infant who lies in a pool of urine on an impervious diaper pad.

In all instances in which an acute dermatitis is present, every effort must be made to remove the soiled diapers as soon as possible after voiding or after a bowel movement. Occasionally in a severe reaction it is worth while to remove the diaper completely. It has been suggested that a gooseneck lamp with a light bulb be placed over the crib, but when weeping of this extent is present, it has been our experience that it is due to secondary pyoderma.

Active Treatment

Further active treatment of a dermatitic reaction in the diaper area must of necessity depend on a careful factorial analysis based on history of onset, morphology and localization. Although there are usually several factors operative in the dermatitic reaction, treatment is directed primarily toward the basic problem.

The infant in whom the seborrheic problem is dominant responds well to Lassar's paste containing 40 per cent sulfur. Our use of sulfur in seborrheic dermatitis is purely empiric. It works well, and the paste serves the double purpose of protecting and treating the damaged skin. Although one might surmise that this quantity of sulfur would produce irritation of the inflamed skin, such is not the case. Locally applied steroids also work extremely well in this kind of inflammatory reaction, and perhaps even a little more rapidly, although not with the same economy. The lesions which occasionally appear on other areas of the skin in association with the seborrheic diaper dermatitis respond well to 2 per cent sulfur, 10 per cent solution of coal tar in a hydrophilic ointment base.

Two preparations are available which are particularly useful in yeast infections: nystatin (Mycostatin) and iodochlorhydroxyquinoline (Vioform). Because of the inflammatory reaction associated with the dermatitis, they are usually used in combination with a steroid: Triamcinolone in the case of nystatin and 0.5 per cent hydrocortisone with 2 per cent iodochlorhydroxyquinoline.

In bacterial infections the treatment of choice is a wide-spectrum antibiotic containing neomycin and bacitracin. The mother must be instructed to cleanse the lesions carefully to remove the crusts, using a soap substitute containing hexachlorophene (pHisoHex). After the cleansing the ointment is applied to the affected areas.

In the occasional infant with allergic contact dermatitis it is essen-

tial to discover the contactant allergen by patch testing and eliminate it. The dermatitic reaction then subsides promptly, but regression may be hastened by using 0.5 per cent hydrocortisone ointment.

In the immunologically normal child, viral infections are self-limited. The only concern is secondary bacterial infection, which may be controlled by neomycin-bacitracin ointment. Compresses using a quaternary ammonium compound (Zephiran 1:1000) are viricidal and may be useful.

CONCLUSION

1. Localization of the dermatitis to the diaper area is determined by specific predisposing and activating factors.

2. Not all diaper dermatitis is caused by the "ammoniacal diaper." Therefore treatment is based on a realistic appraisal of these factors.

3. Distribution, morphology and histopathology support the concept of a diaper dermatitis syndrome.

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MAST CELL DISEASE

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Mast cell infiltration of the skin and other organs characterizes a number of uncommon syndromes.

Urticaria pigmentosa, the most common of these entities, begins early in life with successive cutaneous lesions which typically wheal on trauma and result in persistent pigmented macules or papules.

The term "mast cell disease" has a number of synonyms: Nettleship's disease, xanthelasmoidea, papular erythema, urticaria pigmentosa, urticaria perstans pigmentosa seu hemorrhagica, xanthomoidea urticans, urticaria neviformis, chronolasma urticans, disseminated mastocytoma, mastocytosis, and solitary mast cell nevus.

The first clinical report of urticaria pigmentosa was given by Nettleship[36] in 1869, who reported on a 2-year-old female child with "an unusual form of urticaria." He noted the whealing of lesions following trauma, and described the light brown pigmentation, resembling chloasma, which developed at the site of persistent urticarial wheals.

Sangster[48] (1878) suggested the term "urticaria pigmentosa." Thin[51] (1877) was the first to study the histologic features of the disease, but did not recognize the essential characteristics of the cellular infiltrate. In the same year Ehrlich[16] described the mast cells in his initial scientific publication, pointing out the metachromatic staining of the cytoplasmic granules. In 1879 Ehrlich coined the term "mast cell"[17] (overfed "gemästete" cells), since these cells were most numerous in tissues which he considered to have increased local nutrition, such as chronic inflammation, and tumors.

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The true nature of the infiltrate typical of urticaria pigmentosa was first described by Unna[52] in 1887.

A similar eruption, occurring in an adult, was first described by Liveing[32] in 1881. During the next 68 years sporadic reports of patients with systemic symptoms of mast cell disease consisting of adenopathy, organ enlargement and blood disturbances appeared in the literature, but it was not until 1949 that Ellis[18] documented the systemic nature of mast cell disease by means of an autopsy study. The concept of multi-organ involvement in mastocytosis was then further substantiated by the demonstration of widespread osseous lesions, and other organ infiltration (Sagher,[44] 1952).

MORPHOLOGY AND ORIGIN OF MAST CELLS

The mast cell is a pleomorphic, often irregularly shaped cell, with pale cytoplasm packed with large metachromatic granules which partially obscure the round or oval nucleus.[35]

Mast cells are normally found in various human tissues, particularly in the loose or areolar connective tissue. They tend to be found in groups around blood vessels and are abundant in the synovia. They are present in the dermis, in lymph nodes, in the gastrointestinal tract (especially in the submucosa) and in the wall of the urinary bladder. Although little is known about their origin, it has been suggested that they arise from fibroblast-type stem cells or from undifferentiated cells within blood vessel walls.[21] The inability to demonstrate granular precursor forms has led to an alternate theory that new mast cells are formed by mitotic or amitotic division of pre-existing mast cells or by the elaboration of mast cell granules in other connective tissue cells.[7] Intratracheal instillation of heparin in guinea pigs has resulted in phagocytosis of metachromatic material by the pulmonary histiocytes and monocytes. The subsequent formation of intracytoplasmic granules produces cells mimicking mast cells.[55]

Proper staining of mast cells in tissue sections is difficult. Routine formalin fixation and hematoxylin-and-eosin may result in absent or poor staining of the granules. The cells and their granules may stain well in toluidine blue, methylene blue, methyl green or by Giemsa staining, but even with these dyes results may be somewhat unpredictable.

BIOCHEMISTRY AND PHYSIOLOGY OF MAST CELLS

Histamine is a component of mast cells in animals and human beings,[25, 26] and release of this substance is the apparent cause of urtication of the skin lesions in urticaria pigmentosa. Heparin, a complex

sulfated mucopolysaccharide, is also a constituent of mast cells,[47] and the peculiar basophilic staining properties of the granules have been attributed to this substance, though sulfur-free mucopolysaccharides also may give this staining reaction. Since heparin is an acid mucopolysaccharide and histamine has basic properties, a loose bond between these two substances within the mast cell granule has been suggested.[27]

It has been commonly held that the mast cell itself is the source of the heparin and histamine found within its granules, and thus the cell has been called a "unicellular glandular organ" by Smith and Gum.[49] An alternative theory holds that these substances are formed elsewhere in the body, and only if their breakdown is inadequate are they stored within the mast cell granules.[40]

Serotonin (5-hydroxytryptamine) has been identified as a mast cell constituent in the mouse[37, 40, 47] and rat,[9] but none has been found in dog mast cell tumors[4, 56] or in mast cell-rich tissue from human patients.[26, 47]

Hyaluronic acid, a viscous constituent of the ground substance of connective tissue, is closely related to heparin chemically, but is an acetylated rather than a sulfated mucopolysaccharide. The staining properties of this substance are controversial. The theory that hyaluronic acid is produced by mast cells was proposed by Asboe-Hansen,[60] who felt that heparin and other substances in the mast cell granules act as precursors.

A large number of unrelated substances disrupt or degranulate mast cells in vitro and in vivo, suggesting unusual fragility. These substances include distilled water,[21] ACTH,[4, 56] Tyrode's solution, saline[60] and nitrogen mustards.[4, 49, 46] Ionizing radiation has been reported to damage mast cells,[4, 48, 56] but is also said to be followed by the appearance of increased numbers of mast cells in some animals.[31] Compound 48/80* seems to have a nearly specific effect upon mast cells, degranulation following administration of minute amounts.[21, 22] Probably these agents cause degranulation of the cells without their destruction, since regeneration of granules is rapid. "Ghost" mast cells, nearly impossible to recognize by routine staining, have been shown by radio-autography to take up S-35.[58]

Despite the interesting chemical composition of mast cells, their physiologic function is not known. Histamine and heparin may be released by the mast cell with potent local effects in the surrounding tissue,[31] but there is little evidence that these cells are the principal source of these biochemically active substances, since evidence for their release into the circulation under normal conditions is equivocal. Mast

* 48/80, a condensation product of formaldehyde with paramethoxy-phenylethylamine, Burroughs Wellcome & Co., Tuckahoe, N.Y.

cells may serve as storage centers, with a paucity in their numbers indicative of biochemical deficiencies of these substances.[23]

CLINICAL FEATURES OF MAST CELL DISEASE

The former concept of urticaria pigmentosa as a benign, nevoid syndrome which spontaneously disappears by puberty has been considerably altered by the demonstration of systemic involvement, serious clinical symptoms and occasional fatal termination. Since our knowledge of this disease is in a state of considerable flux, any classification must necessarily be tentative and subject to frequent revisions. Because of the considerable prognostic importance attached to the presence of evidence of systemic involvement, and the lack of knowledge about the exact etiology of mast cell disease, a classification based on type and extent of skin or other organ involvement appears at this time to be appropriate.

Classification of Mast Cell Disease

(Modified from Sagher and Even-Paz[45])

I. *Cutaneous mast cell disease*
   A. *Childhood forms*
      1. Solitary mastocytoma
      2. Bullous urticaria pigmentosa
      3. Diffuse urticaria pigmentosa
   B. *Adult forms*
      1. Diffuse urticaria pigmentosa
      2. Telangiectasia macularis eruptiva perstans
   C. *Generalized mast cell disease*
II. *Polysystemic mast cell disease*
   A. Benign mastocytosis
   B. "Malignant" mastocytosis
   C. Systemic mastocytosis without skin involvement

Cutaneous Mast Cell Disease

CHILDHOOD TYPES. The skin lesions of urticaria pigmentosa are usually noted during the first year of life. The initial skin changes may escape diagnosis, since they are nearly indistinguishable from other kinds of urticaria. Typically, the lesions do not disappear in a few hours, but rather persist for days, weeks or longer, leaving a pigmented macule of the same size and shape as the original wheal. In some patients, erythema may precede wheal formation, while in others the typical macules do not develop until after a number of successive attacks of urticaria.

Single skin lesions (*solitary mastocytoma*) have been reported. These are usually misdiagnosed as nevi, xanthoma, juvenile xanthogranuloma or sarcoma. A prominent clinical feature of solitary lesions of urticaria pigmentosa is the lack of further skin involvement. Sometimes the

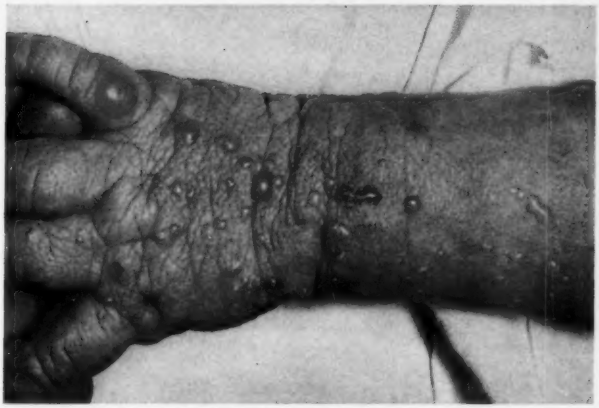

Fig. 62. Clear tension bullae arising spontaneously on the skin of an 8-month-old infant with bullous urticaria pigmentosa.

nodule, which is usually several centimeters in diameter and located on the extremities, may be topped with bullae or vesicles containing mast cells. It is probable that such lesions are found more frequently than is generally reported, and that they resolve spontaneously with time.

The appearance of clear tension blisters on otherwise normal skin may be the first and, in rare cases, the only manifestation of urticaria pigmentosa (*bullous urticaria pigmentosa*) (Fig. 62). This type of eruption is usually found in infants and may cause considerable diagnostic confusion, unless the typical metachromatic granules of the mast cells are seen in smears from the blister fluid.

The skin changes in *diffuse urticaria pigmentosa* develop in attacks, recurrent at intervals varying from days to years, during which the existing pigmented macules wheal, and new areas become involved. Early in its development a typical lesion may be cream- or skin-colored and therefore almost undetectable (Fig. 63). Later, pigmentation deepens from fawn to reddish yellow and even to dark violet-brown. The pigmented macules become nodular, with a chamois-like, velvety surface (Figs. 64, 65). Individual lesions are round or irregularly oval, vary in size from 1 mm. to several centimeters in diameter, and may become confluent to give the skin a "quilted" appearance. Sites of predilection are the face, trunk and extremities. Minor trauma causes typical wheals to appear only on the site of mast cell deposition. The occurrence of factitial urticaria in uninvolved skin surfaces has been reported.

The histologic features of mast cell disease are described in detail on page 894.

Adult Types. *Diffuse urticaria pigmentosa* may develop spontane-

Fig. 63. Macules of urticaria pigmentosa on the arm of a 16-month-old child.

Fig. 64. Widespread distribution of the macular type of urticaria pigmentosa.

ously in adults, from adolescence to old age. Usually the adult forms are maculopapular with symmetric involvement of the trunk, thighs and arms, and relatively little itching or whealing. Spontaneous improvement is uncommon (Fig. 66).

Telangiectasia Macularis Eruptiva Perstans.[59] Crops of persistent reddish macules appear, apparently without cause. There is little pigmentation and frequently no tendency to urtication. The outstanding feature of this condition is the persistent dilatation of the terminal blood vessels, leading to linear or arborescent telangiectases which assume bizarre shapes. The macules involve mainly the trunk and the

Fig. 65. Macular and nodular confluent lesions of urticaria pigmentosa.

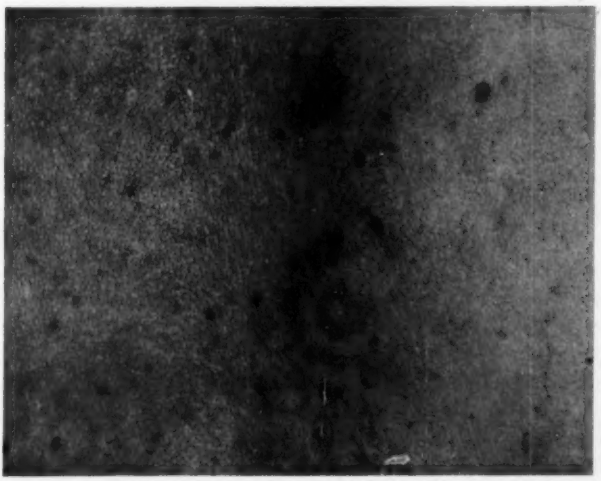

Fig. 66. Deeply pigmented macules of the adult type of urticaria pigmentosa.

extremities, the "telangiectases" the face and chest. Itching and whealing are virtually absent, and the diagnosis is made on basis of the morphology of the skin lesions and the histologic evidence of mast cell infiltration into the skin. Although this rare syndrome is said to occur primarily in obese elderly women, similar lesions have been described in prepuberal girls.

Fig. 67. Scotch-grained "lichenified" skin of a youngster with generalized mast cell disease.

Fig. 68. Diffuse cutaneous infiltrate and bullae in generalized mast cell disease. Two-year-old child with polysystemic, generalized mast cell disease.

GENERALIZED MAST CELL DISEASE. Rarely, mast cell infiltration appears to affect the entire skin. In this type the skin has an "old ivory" tint and is thickened and doughy. The surface may be studded with tiny nodules, making the skin resemble Scotch grain leather. The skin lines are exaggerated, resembling lichenification. This type may be associated with systemic involvement (malignant mastocytic reticulosis—Degos) (Figs. 67, 68).

Polysystemic Mast Cell Disease (Mastocytosis)

In 1949 Ellis[18] reported on a child with urticaria pigmentosa with postmortem findings of mast cell infiltration into many organs, including bone marrow, lymph nodes and liver. He was the first to suggest that urticaria pigmentosa might be part of a polysystemic disease, characterized by mast cell infiltration. Sagher[46] found widespread bone involvement in patients with urticaria pigmentosa, and several reports have fully confirmed dissemination of this disease.

There are now records in the literature of more than 20 patients with the disseminated type of mast cell disease. The salient features of the clinical picture include hepatosplenomegaly, lymphadenopathy, bone rarefaction, skin changes of urticaria pigmentosa and varied peripheral blood abnormalities.

Lymphadenopathy has been noted in approximately half of the patients with severe systemic disease, and tissue mast cells have been present in all patients in whom histologic examinations of the lymph nodes were performed. Hepatosplenomegaly usually develops as the disease becomes progressively more severe.[2, 3] The histologic picture in the liver shows large numbers of mast cells lying between hepatic cells.[3, 24, 33, 39, 50, 57] The degree of splenic and hepatic enlargement may be extreme, with either or both organs extending into the lower abdominal quadrants. Splenic aspiration and histologic examination have shown increased numbers of mast cells, which are rare in normal spleens.[19]

The *bone changes* associated with mastocytosis have been carefully studied by Sagher and co-workers.[45] The roentgenographic picture is that of osteosclerosis and small patchy cystic areas, often resulting in a lacework appearance. There is no deformity of the contour of the affected bone. Changes have been demonstrated in most bones, the ribs being involved in nearly all patients. The x-ray findings resemble those of osteosclerosis of the myeloproliferative diseases and may be confused with those of Paget's disease, but are not diagnostic for mastocytosis. Many of the localized bone changes are of doubtful significance and may disappear spontaneously with time. Aspiration biopsy of the affected area and demonstration of mast cells in the infiltrate are necessary for a definitive diagnosis of mastocytosis of bone.

Bone marrow examination has revealed many mast cells in several patients with mastocytosis, but there is controversy as to whether these cells are normally present in the bone marrow. Ellis[18] found no mast cells in the bone marrow of children with other diseases. Fadem[20] found mast cells in only 7 of 2800 bone marrow aspirates from normal patients and those with various hematologic disorders. On the other hand, Williams,[61] using biopsy particle smears, found mast cells in 17

per cent of 325 patients. Johnstone[30] was able to demonstrate mast cells in 70 per cent of bone marrow aspirates. He considered them to be a normal constituent of the bone marrow and more commonly seen in biopsy sections than in aspirates. Apparently, varying techniques of bone marrow examination explain some of the disagreements among various investigators.

Mast cells have been found in the *peripheral blood* of several patients with severe mast cell disease.[13, 29, 35] In the patients of Efrati et al.[15] and Friedman et al.[24] definite leukemic changes supervened, large numbers of circulating mast cells and immature forms appearing in association with rapidly progressive disease and death. Three other patients died with leukemia of other types, thought to be acute blastic forms in two, and monocytic leukemia in the other.[45] In addition to these severe changes, relative monocytosis and lymphocytosis have been noted in some patients with a tendency toward leukopenia and occasional thrombocytopenia.

Slight alterations in clotting times have been recorded.[12, 14] Whether this abnormality is due to circulating heparin released from the mast cell infiltrates is not known. Urbach et al.[53] applied vigorous massage to the skin of eight patients with urticaria pigmentosa without systemic involvement and observed significant prolongation of clotting times in two patients and increase of protamine titratable heparinoid substances in six. A transitory increase in the clotting time and in lipemia-clearing substances was noted in a patient with systemic mast cell disease after large doses of intravenously administered hydrocortisone.[50] Hemorrhage into the lesions of patients with urticaria pigmentosa without elevated clotting times[5, 10] may be interpreted as indicating that heparin may be released to local tissue areas, without entering the general circulation.

Histamine is contained in high concentration in human mast cells.[26] Brogren[13] reported large quantities of histamine in the urine of patients with urticaria pigmentosa, some of whom had diffuse bone changes. One of these patients had a rise in urinary histamine levels after stroking of a solitary skin lesion. Other investigators[50] could not find histamine in the blood or urine of a patient with systemic mast cell disease during a period without treatment or after either cortisol or nitrogen mustard therapy. Perhaps rapid tissue binding of histamine released by the mast cells prevents it from reaching the circulation.

SYMPTOMS

In view of the high concentration of pharmacologically active substances in mast cells, it is surprising that there are so few symptoms due to the disease. Pruritus is the most common complaint of patients

with urticaria pigmentosa. It usually occurs in areas exposed to some trauma, such as the collar or belt area. In youngsters with disease of long duration, and in adults, itching is not a prominent symptom. Gastrointestinal complaints, particularly diarrhea, have been reported and apparently contributed to the death of the child reported by Ellis. Abdominal pain, flatulence, and vomiting have been reported. Although back and joint pains have been noted, the bone involvement is nearly always asymptomatic. Some patients have been noted to have diffuse flushing of the skin. Hamrin[28] reported a major reaction with hypotension, nausea and vomiting following oral ingestion of salicylate by a patient with urticaria pigmentosa. Salicylate sensitivity has not been observed in other patients, however, and there is no experimental proof that salicylates release histamine from mast cells.

TREATMENT

There is no satisfactory treatment for any form of mast cell disease. It has been generally accepted that the prognosis in urticaria pigmentosa is favorable, with spontaneous involution of the lesions to be expected by puberty. But in view of recent knowledge of the possibility of polysystemic involvement, sometimes progressing to death, a definite prognosis should be withheld pending the results of a thorough general clinical examination and radiologic survey of the skeleton. Examination of bone marrow aspirate and periodic re-examinations should be made in any event.

Even without evidence of invasion of viscera or bones, the distant possibility of serious complications exists. Histamine shock, visceral hemorrhagic tendencies, disturbances of general health due to intractable pruritus, and psychologic upset with difficulty in social adjustment may occur.

In spite of this, and although no extensive follow-up studies have been published, it is the opinion of most observers that the purely cutaneous forms of urticaria pigmentosa spontaneously improve with time, and may disappear, or at least become asymptomatic, by puberty. Urticaria pigmentosa developing in adult life continues indefinitely.

Symptomatic Therapy

Oral administration of antihistaminic drugs may not prevent urtication of the lesions and is unreliable for relief of pruritus. Saunders and Miller found that an intravenous injection of 25 mg. of diphenhydramine hydrochloride (Benadryl) blocked the urticarial reaction.

Cortisone is a potent degranulator of mast cells in man,[1] and mast cell tumors of dogs have regressed under cortisone therapy.[11] Rob-

bins[42] reported good results with ACTH gel in a child with bullous mast cell disease, but other forms of the disease have shown no response to either adrenal steroids or ACTH.[8, 10, 15, 50] Barker[6] reported some response of a patient with systemic mastocytosis following prednisone therapy. Urbach et al.[54] treated 8 children with urticaria pigmentosa with 1 mg. of DOCA sublingually daily, with considerable improvement of pruritus and gradual disappearance of skin lesions during a treatment period extending over several months.

Experimentally, mast cells have been found to be the most radioresistant of any connective tissue cell,[35] and in fact ionizing radiation may result in increased numbers of mast cells.[31] In spite of this, radiation has been reported to improve the skin lesions of urticaria pigmentosa for periods of 10 weeks to 1 year.[29, 34] Involvement of large skin areas makes this form of therapy usually impractical.

Nitrogen mustard is a potent mast cell degranulator and has caused transient improvement in an adult patient with systemic disease.[50] Heparin antagonists, such as toluidine blue and protamine, have given poor results.

SUMMARY

Mast cells, normal constituents of connective tissue, skin and synovia of man, are distinguished morphologically by large cytoplasmic granules which stain metachromatically and contain high concentrations of histamine and heparin. Although these substances are released into the surrounding tissues under a variety of stimuli, it seems that they infrequently reach the circulation, so that their effects are usually localized.

Mast cells have long interested dermatologists as being the salient feature of an unusual pleomorphic chronic dermatosis (urticaria pigmentosa). Although usually found in childhood, adult forms of the disease occur. Recognition of mast cells in tissue sections requires special staining techniques, since the cells may not be recognized in the routine preparations. A valuable diagnostic aid is the response to skin stroking or trauma, which results in whealing of the skin lesions with sparing of intervening areas.

A systemic form of mast cell disease, mastocytosis, has now been adequately documented as a clinical and pathologic entity in both children and adults. Usually associated with some form of urticaria pigmentosa, diffuse radiographic osteosclerosis and hepatosplenomegaly are characteristic manifestations of widespread mast cell disease. The course of this systemic form is variable, but may take on the aspects of malignancy, sometimes with a leukemic component, and terminate fatally. Treatment has been generally unsatisfactory, brief remissions

having been obtained with x-ray radiation, adrenal steroids, DOCA and nitrogen mustard.

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LUPUS ERYTHEMATOSUS

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Some of the various forms of lupus erythematosus have been known for at least 125 years, yet the relation of the cutaneous and systemic varieties to each other, and the causal factors involved in their pathogenesis, are almost as obscure now as they were when the disease was first described.

Rayer[22] (1827) seems to have been the first to describe lupus erythematosus as an entity (*fluxus sebaceous*), although most historians credit Biett[3] (1828—*erytheme centrifuge*) with the original contribution to what has now become a huge and confusing literature.

Hebra[12] clarified the clinical description of the discoid form, and his student Kaposi[14] in 1872 discussed the first patients with constitutional symptoms, stressing the high incidence among female patients, the frequency of joint symptoms, fever, anemia and the fatal outcome.

Although a long drawn-out controversy raged over the etiology of lupus erythematosus, with proponents of a tuberculous etiology arguing polemically in print with the champions of toxins and bacterial infections, Osler[19] described visceral complications of "erythema exudativum multiforme," and Pernet[20] and Libman and Sacks[16] discovered the nonbacterial endocarditis.

Baehr, Klemperer and Schifrin[1] "rediscovered" the systemic form of lupus erythematosus, and first described in detail the vascular changes, particularly those in the kidney. The "wire loop" glomerular capillaries became the pertinent, identifying feature for pathologic diagnosis of systemic lupus erythematosus.

But it was the perceptiveness of Paul Klemperer[15] which pointed out the unifying feature of pathologic anatomy of all affected tissues: the fibrinoid degeneration of the collagen and peculiar alteration of the

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ground substance, producing metachromasia. This led to a concept unifying a variety of acute and chronic maladies, characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components—the concept of "collagen disease."

The discovery of the L.E. cell by Hargraves and his associates[10] made it possible to confirm the diagnosis of systemic lupus erythematosus ante mortem and led to many immunochemical observations. Most recently, the refutation of Ehrlich's "horror autotoxicus" by the increasing evidence for the existence of auto-immune disorders has suggested a tenable hypothesis for the etiology of lupus erythematosus.[7] The indirect demonstration of a widespread disturbance of the body's immune mechanisms as a whole, leading to a tendency to the formation of auto-antibodies against the cellular elements of the blood, and probably also against the vascular endothelium and other tissue components, can be considered to account for the development of the protean symptoms of this disease.

With the emergence of interest of the internists, pathologists, biochemists and immunologists in the systemic form of lupus erythematosus, the common chronic discoid cutaneous type seen mostly by dermatologists was relegated to a minor position. It was even suggested that these two were separate entities, related only by histologic similarity and chance association. But the rare yet well documented occurrence of progression from clinically discoid to acute systemic lupus erythematosus, and the even rarer reverse, as well as the application of intensive laboratory investigation to a large number of patients with the chronic discoid type of the disease, suggested that in fact systemic involvement was more common than was once thought.[9]

Running like Ariadne's thread through the maze of clinical observations on the etiology of all forms of lupus erythematosus is the constant admonition to protect patients against overexposure to direct sunlight.[18, 25] Almost every authoritative report tells of aggravation of the acute systemic variety, and even transformation of chronic discoid into acute systemic lupus erythematosus. On the other hand, critical inspection of published data throws some doubt on such a generalization, since only 15 to 20 per cent of patients give a history of aggravation of their disease after sunburn, and since race, geographic location of residence, and time of year at onset are not related to the intensity of ultraviolet irradiation.

CLASSIFICATION

For many decades it appeared that there were two principal types of lupus erythematosus: one, the "chronic discoid" form, characterized

by scarring skin lesions occurring primarily on the face, ears and scalp, slowly progressive and relatively benign; the other, more uncommon form, characterized by a plethora of systemic manifestations and frequently leading to death. Careful investigation of patients with lupus erythematosus by modern chemical and histologic methods, however, has shown that most of the patients afflicted with the chronic cutaneous types of the disease show signs of a disturbance of many organ systems.[5, 9, 17] For this reason it seems appropriate to suggest that the cutaneous and the systemic forms of lupus erythematosus may be part of a disease spectrum, which may either acutely appear as any one of the clinically recognizable types, or imperceptibly progress from a more benign and localized syndrome to a fulminantly fatal illness.

TABLE 15. *Classification of Lupus Erythematosus*

TYPE	SKIN LESIONS	FEVER, MALAISE	L.E. PHENOMENON	CLINICAL ORGAN INVOLVEMENT
Chronic discoid lupus erythematosus	Always; usually localized	None	Usually negative	Usually *not* present
↓				
Chronic disseminate lupus erythematosus	Always; may be diffuse	Sometimes	Usually negative	Usually *not* present
↓				
Subacute systemic lupus erythematosus	Usually, often on extremities	Frequent	Usually positive	Frequently present
↓				
Acute systemic lupus erythematosus	Sometimes	Almost always	Almost always positive	Always present

INCIDENCE

The primarily cutaneous (chronic discoid and chronic disseminated) forms of lupus erythematosus are extremely rare in infancy and childhood, but may sometimes be found in older children at or near puberty. In a recent study[6] only 2 per cent of 100 patients with chronic discoid lupus erythematosus were less than 10 years of age, and only 12 per cent less than 20 years. Although the incidence of the chronic cutaneous forms has changed only little in the last 3 to 4 decades, there has been a progressive increase in the number of cases of the systemic types reported in the past 10 years. A good example of this perplexing phenomenon is seen in a report of 37 cases of acute systemic lupus erythematosus in children under 14 years of age seen over a 46-year period at the Children's Hospital in Boston, and in a

recent 6-year period at the Children's Hospital in Cleveland. The authors report that 80 per cent of the youngsters affected were seen since 1950![6]

The great preponderance of both cutaneous and systemic types of lupus erythematosus in female patients (approaching 70 to 90 per cent in the larger groups studied) has been previously commented on. There is no demonstrable racial predilection. Instances of familial occurrence of lupus erythematosus in siblings[4] and in families in which other members had the chronic or discoid type of rheumatoid arthritis have been reported.[11]

ETIOLOGY AND PATHOGENESIS

Physical, chemical and bacterial agents have been incriminated in the pathogenesis of lupus erythematosus, but so far substantial evidence for a causal relation with any of these is lacking.

For years the disease was considered to be of tuberculous nature, mainly because active tuberculosis was frequently found on autopsy, and because the name "lupus" still causes confusion in the mind of many observers. At the turn of the century, toxins related to bacteria were regarded as a cause, and soon after Barber[2] suggested a relation to hypersensitivity to streptococci. Later studies demonstrating the absence of bacteremias and predominantly normal serum antistreptolysin and streptococcal antihyaluronidase titers militate against this concept.[21]

The great frequency of untoward reactions to drugs, vaccines, serums and transfusions and the frequency of anticomplementary and biologic false-positive serologic tests for syphilis lend support to the hypersensitivity theory of causation. The most recent concept of "autoimmune disorder"[7] is based on the finding of hematologic abnormalities (positive Coombs test, hemolytic anemia, idiopathic thrombocytopenic purpura, leukopenia, positive serologic tests for syphilis, circulating anticoagulants and presence of the L.E. factor). The frequency of abnormal globulins, and the rapidly increasing incidence somewhat paralleling widespread use of potentially sensitizing chemotherapeutic agents, suggest that the entire disease picture (at least of acute systemic lupus erythematosus) may be a complex of immunologic disturbances affecting blood cells, other blood constituents and small blood vessels.[7]

CLINICAL FINDINGS

Localized Cutaneous Types

Chronic discoid lupus erythematosus usually begins with one or several small erythematous scaling macules. These are sharply marginated, and

Fig. 69. Early papular and hyperpigmented lesions of chronic discoid lupus erythematosus in a 13-year-old Negro girl. Note papules at borders, and polycyclic configuration.

Fig. 70. Late scarring lesions of chronic discoid lupus erythematosus in an 11-year-old boy. Note "worm-eaten" atrophy of external ear and depigmentation and telangiectasia in the cheek lesion.

soon develop an elevated "ring-like" border. The lesions extend slowly over a period of months or years, usually around the entire border. A grayish adherent scale develops, which extends into the follicular openings of the skin (carpet-tack scale) (Fig. 69). Keratotic "plugging" of the follicles is a striking feature both clinically and histopathologically. As time passes, gross evidence of atrophy appears. This is more noted in the central parts of older lesions and is often associated with loss of

pigment and telangiectasia (Fig. 70). The lesions do not ulcerate and are generally asymptomatic. Coalescence of smaller patches may give rise to bizarre, gyrate patterns. The sites of predilection are the cheeks, nose and scalp. Scarring alopecia follows lesions on the scalp. Involvement of the eyelid margins may cause loss of cilia and ectropion. Common, but often overlooked, sites are the external ears and ear lobe. Here the process causes a "worm eaten" appearance, and hyperpigmentation is common.

The chronic disseminated type shows similar lesions to the ones described above, but distributed more widely over the V of the neck and back and the skin over the shoulders and upper arms. Exacerbations and remissions occur spontaneously, and it is not uncommon to see old scarred lesions with evidence of new activity (dusky erythema, nodules and papules) at the borders.

Chronic discoid lupus erythematosus is uncommon in children, occurring after puberty when it is present. Confirmation of the clinical diagnosis by histopathologic examination of small punch biopsies is necessary and is simple.

Acute and Subacute Systemic Lupus Erythematosus

The clinical features of systemic lupus erythematosus are extremely varied. As in adults, prodromal symptoms of malaise, arthralgia, intermittent fever, renal disease and thrombocytopenic purpura may occur individually or together, and suspicion as to the true diagnosis may not be raised for months or even years because of the protean manifestations and gradual development of symptoms. Frequently the disease is first diagnosed as rheumatic fever, rheumatoid arthritis, chronic infection or nephritis. The initial spontaneous remissions of most symptoms further compound the confusion about the proper diagnosis. As a rule, the children rather rapidly become seriously ill within six months to one year after onset of the first symptoms. About 10 per cent of patients present with a fulminant type of this disease and die within 3 to 6 months in spite of all therapy.

Skin Lesions

In approximately one third of all patients, skin involvement is noted as one of the presenting symptoms. Although there is satisfactory proof that some patients may go through the entire course of the disease without cutaneous manifestations, more than 80 per cent sooner or later have some form of skin eruption. The classic facial eruption, present in 30 to 50 per cent of patients, begins as an erythematous macular flushing covering the malar areas and extending over the

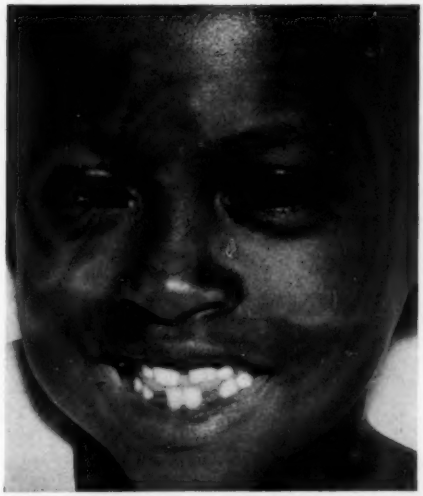

Fig. 71. Malar erythema and depigmentation without nodule formation. Acute systemic lupus erythematosus in a 9-year-old child.

Fig. 72. Papulonodular erythematous lesion on the cheeks. Acute systemic lupus erythematosus in an 11-year-old boy.

bridge of the nose (Figs. 70, 71). The lower eyelids may be involved, but the upper lids are usually spared. The erythematous areas may become elevated, smooth plaques with nodular irregular thickenings (Fig. 72). There is no atrophy and usually no clinical follicular plugging. With time, the lesions may become vesicular or bullous; they may necrotize, leaving behind deep, secondarily infected ulcers. Hemorrhage into the nodules and bullae may be present. Often the entire face is

Fig. 73. Typical erythematous maculopapules along fingers and on thenar eminence. Acute systemic lupus erythematosus of fulminant type.

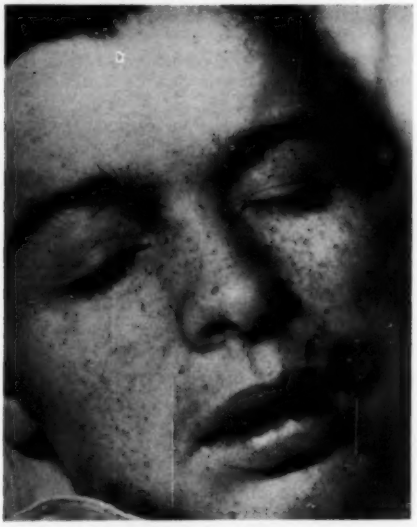

Fig. 74. Petechiae and lip ulcerations in acute fulminant systemic lupus erythematosus.

progressively involved, and occasionally the scalp, neck and extensor surfaces of shoulders and upper arms are affected. Biopsy of the lesions shows the typical histopathologic picture of lupus erythematosus (see p. 910). The distribution is usually symmetrical, and in the macular or nodular stage the lesions are asymptomatic.

The second most characteristic cutaneous changes are intensely erythematous macules appearing about the nail bed, along the sides

Fig. 75. Diffuse, patchy, nonscarring alopecia accompanying systemic lupus erythematosus in a 9-year-old girl.

of the tips of the fingers and toes and on palms and soles (Fig. 73). These macules may become purplish and petechial, and ulcerate to heal by stellate scarring. Splinter hemorrhages of the nail bed and acute abacterial paronychias are common.

Petechial eruptions (accompanying thrombocytopenic purpura), urticarial lesions, erythema nodosum and subcutaneous nodules over the extensor tendons of the hands, wrists and patella are occasionally noted.

Mucous membrane lesions, consisting of gingivitis, buccal petechiae, small ulcers of the mouth and lips and vulvovaginitis are common (Fig. 74).

Partial, motheaten, temporary alopecia is found in about 20 per cent of children (Fig. 75). Regrowth of hair may follow steroid-induced remissions.

Systemic Manifestations

Fever, varying from mild to extreme temperature elevation, is found sooner or later in all patients. Arthralgia and frank arthritis occur in the majority, and are presenting symptoms in about half of the children. Cardiac involvement, hypertension, hepatomegaly or splenomegaly and renal disease occur in one third to one half of all patients. An excellent account of the details of the systemic manifestations,

their course and pathologic features can be found in the classic monograph of Talbott[24] and in the recent report of Cook et al.[6]

Briefly, the most serious problems encountered are the renal involvement (pyelonephritis, renal failure), cardiac abnormalities leading to heart failure and pericarditis, and central nervous system symptoms (convulsions, hemiplegia, cerebral vasculitis).

Acute bacterial infections, bleeding phenomena and severe transfusion reactions pose common intercurrent problems in management.

LABORATORY FINDINGS

Chronic Discoid and Chronic Disseminated Lupus Erythematosus

In several large series of adult patients carefully studied the most significant deviation from normal was found in serum protein analysis. About 40 per cent of patients have elevated gamma globulin levels; next comes elevation of the beta globulin fraction. L.E. phenomena are negative in the vast majority of these patients, irrespective of the method used. Coombs tests, urinalysis and white blood cell counts are usually normal. About 20 per cent of patients have an elevated sedimentation rate. The histopathologic examination of skin biopsies is usually the most reliable diagnostic procedure (see p. 910).

Acute and Subacute Systemic Lupus Erythematosus

The importance of the *L.E. phenomenon* for the diagnosis of systemic lupus erythematosus can be appreciated by the fact that more than 95 per cent of all patients show a positive L.E. test some time during the course of their disease. The L.E. cell can be demonstrated in the bone marrow, but is more easily found in the buffy coat of minimally heparinized venous or capillary blood. There are at least three components necessary for development of this phenomenon: a *plasma factor*, apparently residing in the patient's gamma globulin, which appears to be an immunologically distinct substance; *nuclear material* derived from polymorphonuclear leukocytes; and *phagocytic cells*. A single swollen phagocyte with engulfed nuclear material is an L.E. cell; a cluster of such cells about lysed nuclear material produces a "rosette" (Fig. 76). Of the three components, the serum factor must come from a patient with systemic lupus erythematosus, but the nuclear material and phagocytic cells may come from normal patients or even animals (dog marrow). *Coagulation* accentuates the reaction; hence minimal or no heparinization is necessary, and sufficient *time* must elapse for the reaction to take place. The serum L.E. factor may be demonstrated in

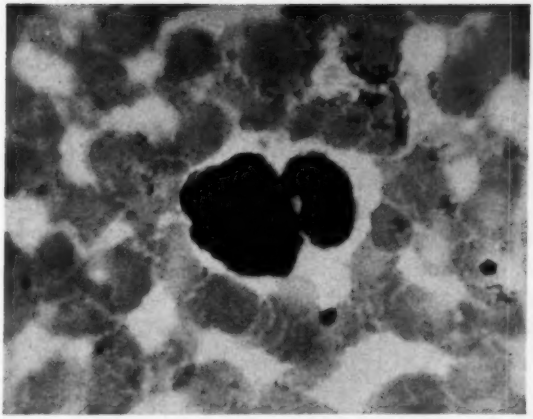

Fig. 76. Typical L.E. cell showing engulfed nuclear material in a swollen phagocyte. Buffy coat preparation.

body fluids, effusions, blister fluid and even urine. Biologic false-positive L.E. tests are extremely rare. Therapy with corticosteroids may or may not reverse the L.E. phenomenon, and sometimes repeated serial tests are necessary before a positive preparation is found. The presence of a positive L.E. test strongly favors a diagnosis of systemic lupus erythematosus.

A normochromic, normocytic *anemia* is generally found early in the development of the disease, and becomes progressively more severe. Reticulocyte counts are usually normal. An obvious hemolytic component (positive Coombs test or hemagglutinins) frequently contributes to this anemia.

Leukopenia is present early in about two thirds of all patients, and frequently becomes progressively more severe. *Thrombocytopenia* occurs in 15 to 20 per cent of the youngsters and may lead to thrombocytopenic purpura, which may be the presenting symptom. *Reversal of the albumin-globulin ratio* with electrophoretically significant increase in the $alpha_2$ and gamma globulins is frequently noted. This disturbance of the plasma proteins is thought to be responsible for positive cephalin-cholesterol flocculation, thymol turbidity, thymol flocculation or biologic false-positive serologic tests for syphilis. *Heterophile antibodies* may be present in high concentrations.

The majority of patients show definite evidence of *renal involvement*, evidenced by increase in urinary protein excretion, hematuria, leukocyturia, and later azotemia, acidosis and electrolyte imbalance.

Electrocardiograms often show abnormalities, usually depression of the T waves and atrioventricular conduction defects.

THERAPY

Chronic Discoid and Chronic Disseminated Lupus Erythematosus

Until the early 1950's, treatment of the chronic scarring types of lupus erythematosus was generally slow and unsatisfactory. Gold salts, arsenic and local destruction were variously favored. The beneficial activity of quinine was reported late in the last century. The most significant advance in therapy came with the introduction of the newer synthetic antimalarials, Mepacrine and Chloroquine. At present Chloroquine and mixtures of antimalarials (Triquin) are most widely used. The usual starting dose for adults ranges from 500 to 750 mg. per day, with proportionately smaller doses for children. Side effects from this form of therapy are generally minor. Blurred vision and nightmares represent minor central nervous system toxicity, and disappear on lowering dosage. Granulocytopenia, drug eruptions and gastrointestinal upsets have occasionally been reported. The most significant toxic reactions to date are those due to deposition of the drug in the lens capsule, causing difficulty in vision, diffraction errors, and reversible opacities. These are not usually a significant hazard unless large doses or prolonged administration of the drug is utilized.[13]

The effect of the antimalarials is primarily suppressive and temporary. Although 80 per cent of the patients show moderate to striking responses to antimalarial therapy, consisting in cessation of progression, involution of nodules and flattening and healing of lesions, relapses on cessation of treatment are common, and long-term maintenance therapy is usually necessary.

Acute and Subacute Systemic Lupus Erythematosus

Recent reports demonstrate that the mortality in systemic lupus erythematosus, particularly in children, is still very high.[6] There is at present no specific, consistent therapy for systemic lupus erythematosus. The introduction of the adrenal corticosteroids has resulted in provision of symptomatic remissions, however, and sometimes even prolonged arrest of the disease process.

The use of large doses of ACTH and other adrenal corticosteroids may be temporarily lifesaving and induce clinical and biochemical remissions. As a rule, intravenous administration of ACTH by eight-hour drip produces the most dramatic effects. Subsequent change to the newer synthetic corticosteroids with lesser side effects is indicated. Prednisone, Triamcinolone, Dexamethasone and their analogues all have their adherents. As a rule, maximally tolerated doses, sufficient to induce clinical remissions without evidence of serious toxicity, are indicated. Very gradual reduction of dose to the point of recurrence

of mild symptoms, and maintenance at this level may significantly prolong life. The simultaneous administration of corticosteroids and Chloroquine may allow use of lower steroid doses for maintenance.

Experimentally, whole body radiation, nitrogen mustard, 6-mercaptopurine and other cytotoxic agents have been used in an attempt to stop the auto-antibody production.[8, 23] At present these heroic measures must be considered experimental and reserved for last-ditch stands.

Supportive therapy is of course indicated, depending on the organ system primarily involved.

SUMMARY

Lupus erythematosus is a peculiar, multisystemic disorder variously affecting the skin and most other organ systems. Clinically, two principal types occur: one primarily involves the skin of the exposed surfaces and runs a benign course; the other is often fulminant and pansystemic. There appear to be all sorts of transition forms, leading most observers to believe that these are all manifestations of one disease process.

The disease predominates in female patients and is uncommon in childhood. The etiology is still unclear, but most recent evidence suggests that it is an expression of an auto-immune disorder, triggered by trauma, drug sensitization or some sort of self-intoxication. Therapy is primarily suppressive, and the prognosis in the systemic form is poor.

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CONCEPTS OF DERMAL PATHOLOGY

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The purpose of this report is to present concepts, principles and contributions of dermal pathology to the specialty of dermatology and medicine in general. A review of such aspects as role of the dermal pathologist, infallibility of the dermal pathologist, value of biopsy, selection of biopsy site, methods of biopsy, completion of biopsy request, and processing of tissue, seems pertinent. To point up specifically the values of a dermal pathologist to pediatric dermatology, the following will be presented: the histopathology of some problem cutaneous diseases, along with differential diagnosis, and a large clinicopathologic study in which the diagnosis is always made by the dermal pathologist.

ROLE OF THE DERMAL PATHOLOGIST

It is the practice of most workers in the basic and life sciences to consult each other freely and, if problems arise, to seek out experts in their respective fields when assistance is required. This philosophy should exist among all physicians regarding patient referral and sending of material for special studies. All physicians dealing with the diagnosis and treatment of cutaneous diseases should preferably send their biopsy material to a qualified dermal pathologist, be he a dermatologist or pathologist.

The skin is a vital complex organ, and the many diseases that can afflict it are easily verified by reference to any standard dermatology textbook. Those physicians with special interest in and knowledge of

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The author wishes to acknowledge with appreciation the Armed Forces Institute of Pathology as the original source of many of the photomicrographs.

dermal pathology can best interpret the pathologic changes in many of these diseases. Some features, although minute, are important and may be easily missed by the inexperienced observer. Expert knowledge of clinical dermatology is also necessary so that gross and microscopic changes can be correlated in arriving at the correct diagnosis. Examples of this are when the dermal pathologist interprets the bleeding points of Auspitz phenomenon in psoriasis as due to thin suprapapillary plates and considers that the fine wrinkled cigarette paper scale of pityriasis rosea is caused by spotted parakeratosis. The importance of correlating gross and microscopic changes is especially true when dealing with inflammatory diseases, unusual tumors, lymphomas and reactive processes involving the skin. The role of the dermal pathologist in the field of research must not be overlooked. The many excellent clinicopathologic and basic research studies published by dermal pathologists verify this role. As a result of this we have a better understanding of the natural history of many diseases along with knowledge of the dynamics, etiology, histogenesis and pathogenesis. The role of teaching is important and is emphasized by the mandatory requirements of some of the American Specialty Boards which require a basic working knowledge of dermal pathology before a candidate can be certified. Perhaps the greatest role the dermal pathologist has rendered to dermatology is the tendency to direct interest from one of speculation down to facts.[8]

INFALLIBILITY OF THE DERMAL PATHOLOGIST

Is the dermal pathologist infallible? The answer, of course, is no. Recent papers by Desjardins[6] and Wartman[17, 18] discuss this subject in an excellent manner, and their viewpoints are applicable to the field of dermal pathology as well as general pathology. Desjardins feels that microscopic examination of sections of tissue, when carried out by a pathologist who has had superior training and long experience, is a most valuable method of determining the essential nature of an inflammatory process or of identifying different kinds of benign or malignant tumors. But because it is the best method available, it must not be inferred that a pathologist's interpretation of tissue changes or his opinion about the identity of a tumor is always accurate. The fact that sections of tissue are examined through a microscope does not eliminate the human element of the pathologist himself. The pathologist cannot possibly be infallible and should not be expected to bear the sole responsibility for the identification of disease processes. If this is kept firmly in mind, it behooves the physician to analyze closely the history of the patient's illness, its clinical features, and the physical and x-ray findings, and to correlate these with

the pathologist's findings. Finnerud[8] states that we all agree that at times clinical judgment supersedes histopathologic findings.

Wartman[18] conceives that pathologists are not infallible, but on the contrary, are earthbound devils like the rest of the medical profession. In assessing the validity and reliability of histopathologic diagnosis, he alludes to the conditions under which we now work. He feels that the nature of biopsy diagnosis is probably changing and that under these new conditions microscopic diagnosis may not have the same degree of validity and reliability that it had in the past. Today we are being confronted with specimens that are either very small, at times consisting only of a few isolated cells, or in which the lesions are slight or minimal. Under these changed conditions it is necessary that we keep clearly in mind the chief purpose of doing a biopsy, which is to collect as objectively as possible the histopathologic evidence of a disease and then to evaluate this in light of the patient's illness. Objectivity in making histopathologic diagnoses and careful and honest correlation with the subsequent clinical course of the patient are proved ways of adding to knowledge that we should not lightly discard. The changed nature of biopsy material makes it more desirable than ever before to obtain information about the degree of consistency of each observer's microscopic diagnoses and the variations that exist in the diagnoses of different observers.

THE VALUE OF BIOPSY

According to Wartman,[17] over the past century physicians have gradually accepted the biopsy as a reliable and accurate way of obtaining useful evidence to support the clinical diagnosis of disease. The dictionary definition of biopsy is "the visual examination of material removed from the living body for the purpose of diagnosis." The term "biopsy" is taken from Greek (βιος, meaning life, and Οπσις, meaning vision) and was coined by the French dermatologist Ernest Henri Besnier in 1879, although, earlier, Virchow had emphasized the fundamentals and indications. Initially it was hailed as a great medical advance, but after the enthusiasm of the originators of the method had died down, most investigators thought little of the method. During the latter part of the nineteenth century and the first half of this century the usefulness of biopsies was viewed with renewed interest and was used by increasing numbers of physicians. Today the accuracy and reliability of biopsy diagnosis have become so widely accepted that diseases are reported in journals as being "proved by biopsy." Only a few aids to clinical diagnosis enjoy this amount of prestige.

The chief contribution of a biopsy is to provide histopathologic

evidence of the nature of the patient's disease. Finnerud[8] states that a well prepared section from a biopsy specimen taken with good judgment will put to rest many fancy speculations.

SELECTION OF BIOPSY SITE

According to Caro,[4, 5] selection of the biopsy site is of vital importance and should not be delegated to an inexperienced assistant. In keeping with the suspected clinical diagnosis, the examiner should search for characteristic lesions whose appearance, consistency or configuration will be of help in establishing a diagnosis. Those lesions that are inadequately developed, involuting or show effect of trauma or previous treatment should be avoided. It is futile to expect much help from a biopsy of a lesion that is too young, too old or too damaged to be diagnostic. A histopathologic examination will not endow a lesion with characteristics it does not already have.

If possible, the biopsy should be taken from a location that the disease under consideration commonly involves. If several kinds of lesions are present, a specimen should be obtained from each for comparison, and also to determine whether more than one disease is present. In most diseases it is preferable to take the biopsy from inside the boundaries of the lesion so that only pathologic tissue is submitted for examination. In some instances it is well to remove the biopsy specimen from the border of the lesion so that a small amount of normal tissue will be included. The presence of some normal tissue allows for study of the advancing border of the pathologic changes, and is useful in evaluating some disease processes. Before such a specimen is removed from the skin it should be marked properly with indelible pencil or methylene blue to delineate both the normal area and the lesion itself. Failure to do this may result in faulty bisection of the specimen into a normal and a pathologic piece and can lead to confusion.

METHODS OF BIOPSY

Methods of skin biopsy technique have been reported in recent years by Caro[4, 5] and Whyte and Perry.[10]

The skin at the site selected should be cleansed properly with soap and water and sterilized by the application of alcohol or Zephiran solution. Local anesthesia may be produced by injecting a 2 per cent solution of procaine. For very small lesions or pedunculated ones, the injection of a local anesthetic may not be necessary, for sharp instruments and a rapid technique may make the procedure relatively painless.

For most lesions the preferable method of obtaining a suitable specimen is cold-blade removal, although any orthodox surgical method is adequate. An excised specimen may be readily sectioned in the correct plane vertical to the skin surface. The type and depth of the lesion to be biopsied will often determine the kind of surgical procedure that is required. When specimens of vesicles and bullae are obtained for histopathologic examination, it is important that the entire lesion be removed intact. This permits evaluation of the location of the blister, appearance of the roof and floor, and type, condition and staining reactions of cells in the fluid contents.

Small specimens of all types may be removed by the use of a cutaneous punch. This is drilled through the skin to the desired depth, and the separated specimen is lifted from its site and cut off at the base with a scalpel or scissors. The cutaneous punches used most often vary in size from 2 to 6 mm., and the resulting wound seldom needs suturing. Whyte and Perry[19] recently reported a simple method to minimize scarring following large punch biopsies. Digital traction is applied perpendicular to the lines of greater skin tension on either side of the biopsy site. Release of added lateral digital tension after the specimen has been removed permits normal skin tension to deform the circular defect into an easily sutured ellipse. Most of the time, suture of this wound is possible without puckering. For the small punch biopsy wounds, a disk of absorbable gelatin sponge (Gelfoam) cut to fit the size of the defect is applied, and the wound is covered with a dry dressing. The use of a high-speed power-driven biopsy punch has advantages because it is relatively less painful than the manual procedure. When little or no tissue alteration is desired, this procedure is valuable because it may be performed without the use of local anesthesia. For experimental work such as obtaining specimens for electron microscopy, and those necessitating multiple and repeated biopsies, this method has considerable value.

A small, sharp curet will often obtain sufficient material for a diagnosis. For larger and deeper biopsies an elliptical excision with a scalpel should be performed and the wound closed with sutures. Pedunculated lesions may be clipped off with scissors, but an attempt should always be made to include the base of the lesion in the specimen. Electrosurgery should not be used in performing a biopsy on the skin because of the risk of burning the specimen. The tissue may show changes of cellular distortion and alteration of the staining reactions. The specimen should never be removed from the skin with forceps or any instrument that would alter its normal relations. It may be removed with a needle, curet or scalpel, and if large enough to curl, should be flattened on a card before being dropped into the fixative solution. A specimen that is squeezed or twisted before fixa-

tion will produce sections so distorted that no useful information can be gained.

Special procedures such as Tzanck and touch smears should be obtained as follows (these are of diagnostic value in vesicular, pustular, and bullous diseases of the skin): Smears are made by gentle scraping of the base and under side of the bulla roof with a number 15 Bard-Parker blade or other acceptable instruments. The material obtained is smeared on clean dry slides, and inserted into an appropriate fixative. The touch smear technique is of value for rapid presumptive diagnosis of malignant tumors. At the time of obtaining a biopsy for routine processing, the fresh tissue is bisected and quickly touched or smeared on clean dry slides, and fixed immediately in an acceptable solution. Valuable data can be obtained from these procedures and, when correlated with the gross pathology and routine sections, can often aid in arriving at a more definite diagnosis.

BIOPSY REQUEST

It is important that each specimen be placed in a separate bottle and identified properly. The same holds true for properly labeling Tzanck and touch smears. A pathology examination request form should be filled in completely and submitted with the specimen or slide. Pertinent information should include name, age, sex and color of the patient. Adequate clinical information should include duration, biopsy site, proper description, type of lesion, number, distribution, stage (acute or chronic) and symptoms. If pertinent, past history such as treatment, results of previous biopsies, and family history should be listed. A constructive clinical differential diagnosis should be indicated in order of suspected preference. All this information is important for the dermal pathologist to arrive at a final interpretation. In difficult problems the clinical information may be of aid in deciding whether the microscopic findings are compatible or incompatible with any of the diagnoses under consideration.

PROCESSING OF TISSUE

Every pathologist has his favorite routine fixative, and no doubt each has its advantages for certain tissues and problems. It has been the practice in our laboratory to use a 10 per cent buffered neutral formalin solution as a routine tissue fixative. Fixatives such as Bouin's fluid, Zenker's fluid and others are not satisfactory because they tend to harden the skin. As a result of alteration and distortion of the tissue there is always a chance of possible error in diagnosis. Special fixatives may be helpful for specific enzyme studies, mast cell granules,

electron microscopy, and demonstration of certain inorganic and organic compounds. For Tzanck and touch smears, absolute alcohol, methyl alcohol, 50 per cent ether-alcohol or Cyto-Dri-Fix (Paragon) are adequate fixatives. The last is of particular value because it dries rapidly and will allow for shipping or storage of the slides for processing at a later date.

Specimens are bisected whenever possible, and one half is processed in paraffin, while the other half is kept in reserve for special studies if such are indicated.

The examination of small specimens calls for special care, so that the lesion will not be missed in cutting the sections. In some cases both small and large specimens require serial sections before locating the pathologic portions. This is particularly true in inflammatory diseases in which only a few cuts would show the diagnostic features and the remainder appear nondiagnostic. In studying large specimens it is important to examine sections from various parts of the specimen. In tumors, particularly when excised, representative sections should be taken in the proper plane so as to check adequacy of removal. The transverse plane in one to three areas of a tumor will usually allow for adequate evaluation as to complete or incomplete removal. Sections deeper in the tissue block are recommended when a disease is suspected and the findings are inconclusive. At times repeat biopsy specimens are required to confirm an impression or because the initial specimen was inadequate for diagnosis.

One factor that is indispensable to good work in dermal pathology is the contribution made by the tissue technician. We are reminded of our great indebtedness every time we are called upon to examine a section prepared by technicians less skilled in the processing of cutaneous specimens. The technicians in most general hospital laboratories are not aware that the skin is an extremely hard and difficult tissue to process. They generally are accustomed to handling large specimens of soft tissue, and processing comparatively small punch biopsies of skin often results in sections that are embedded wrong, cut tangentially, or are thick, overstained, wrinkled and folded. Study of sections like these too frequently leads to a histopathologic diagnosis of chronic dermatitis or "inflammation." For the relatively precise work of a dermal pathologist, it is essential to have technicians who are specially trained, interested in their work and scrupulous in processing specimens that may range in size from large masses down to minute fragments. The sections should be thin (5 to 7 microns), evenly cut, spread smoothly on the slide, and skillfully stained. Sections of high technical quality allow a much better opportunity for definitive interpretation.

Hematoxylin and eosin is used as a good routine stain. When in-

dicated, special procedures are used to demonstrate melanin, iron, calcium, glycogen, mucin, colloid, amyloid, fat, collagen fibers, reticulum fibers, elastic fibers, muscle, blood vessels, nerve, fungi, spirochetes, protozoa and bacteria. Vital staining is useful to demonstrate amyloid and mast cells. Giemsa's stain is most commonly used for Tzanck smears and Papanicolaou's stain for touch smears. Polariscopic examination is of value when foreign material such as silica, talc, and wood slivers is suspected and for cholesterol esters. Darkfield illumination is used to check for the presence of silver. Microincineration and fluorescent microscopy are useful in specific instances.

DERMAL PATHOLOGY OF SPECIFIC DISEASES

In the remainder of this report I would like to cite specific instances in which the role of the dermal pathologist is extremely valuable and often the only means of arriving at a definite diagnosis. This is particularly true in the field of pediatric dermatology, in which there may be considerable variation in appearance of the same disease in children and in adults.

Mast Cell Disease

This is the subject of one of the papers making up this symposium (see p. 857). Regardless of the different morphologic types as listed in the classification, there is always one thing in common, that of the mast cell. Because of clinical variations in the number of lesions and morphologic appearance, mast cell disease can often lead to confusion with other diseases. Even the best clinicians and pathologists may at times have difficulty. Microscopic examination of hematoxylin- and eosin-stained sections under the scanning and low-power objective usually reveals a normal epidermis except for some increased melanin in the cells of the basal layer. The exact reason why cutaneous lesions are sometimes pigmented can probably be explained in part by the presence of melanin, but not entirely. Some lesions may be clinically pigmented, but the basal layer of the epidermis is relatively free of melanin on microscopic examination. The pigmented color observed clinically is then probably due solely to the accumulation of mast cells in the dermis. Most often this mast cell infiltrate is diffuse throughout the dermis, although in some types the cells are localized predominantly about the subpapillary capillaries (Fig. 77). Even in the more diffuse type many of the mast cells surround the vessels. It is not unusual to see a thin normal band (Grenz zone) of collagen between the epidermis and mast cell infiltrate. Under high power the mast cells can be recognized as those with an oval, fusiform or spindle ap-

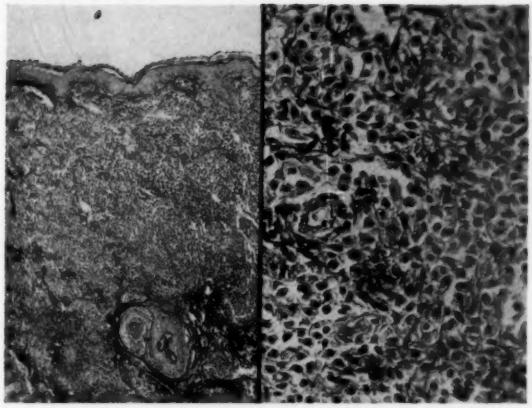

Fig. 77. Masson's trichrome stain showing a diffuse mast cell infiltrate in the dermis. The cells are oval or slightly fusiform and contain a round to ovoid nucleus. Cytoplasmic granules are present. There is thinning of collagen fibers. Composite magnifications, × 50 and × 300.

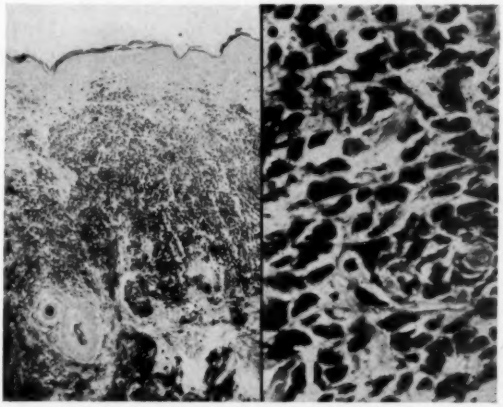

Fig. 78. Giemsa's stain to show metachromasia of mast cell granules and their fusiform or spindle shape. Composite magnifications, × 50 and × 575.

pearance (Figs. 77, 78). The nuclei are round to ovoid and stain basophilic with hematoxylin and eosin (Fig. 77). The cytoplasm is eosinophilic and filled with fine, pale purple granules, although at times these are difficult to demonstrate. This is particularly true when the lesion has been irritated or traumatized before biopsy. This is one of the instances in which confusion with other cutaneous diseases might be accounted for because, without granules, the mast cell may appear as a histiocyte, reticulum cell, nevus cell, melanoma cell or one of the lymphocytic series. The cell boundaries may be indistinct, particularly

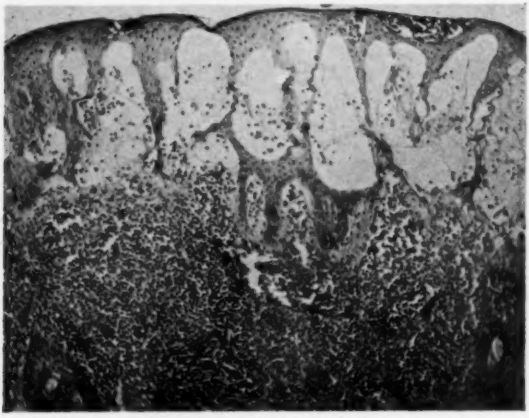

Fig. 79. Bullous form of mast cell disease. × 90.

when their shape is irregular or fusiform. It is not unusual to find numerous eosinophils intermingled with the mast cells, particularly when there is interstitial edema or bullae formation. The presence of eosinophils may be related to histamine release. When bullae are present, they are usually subepidermal, although in severe examples there may be intercellular edema and vesicle formation within the epidermis (Fig. 79).

In a recent investigation with Dr. Elson B. Helwig,[9] special histochemical procedures and electron microscope studies of the mast cell were performed working with tissue (skin) obtained from two patients (one infant and one young adult) with systemic mastocytosis. With Giemsa's method and toluidine blue the cytoplasmic granules stained metachromatic. Acid mucopolysaccharide (AMP) and alcian blue techniques revealed positive material in the cytoplasm, identifying it in part as an acid mucopolysaccharide. Prior digestion of sections with bovine testicular hyaluronidase for one hour failed to remove this positive material from the cytoplasm and in part tends to rule against the presence of hyaluronic acid. By utilizing the aldehyde-fuchsin method the material was further identified as a sulfonated acid mucopolysaccharide which is the biochemical makeup of heparin. Periodic acid-Schiff-positive material was present in the cytoplasm of the mast cells. Prior digestion with diastase failed to remove this material, ruling out the presence of glycogen, and probably indicated the presence of less sulfated forms of heparin, although the presence of a glycoprotein, mucoprotein or neutral mucopolysaccharide cannot be ruled out. Fontana-Masson stain for argentaffin granules gives a negative reaction, and this supports the absence of serotonin in human mast cells. Johnson and Helwig[13] have used this procedure with nega-

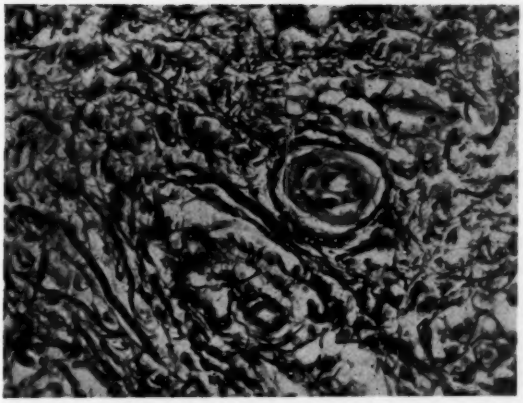

Fig. 80. Snook's silver stain shows a dense network of reticulum fibers around the mast cells and capillaries. × 485.

tive results on tissue sections from 12 children with isolated mastocytosis of the skin. Special stains for iron were negative. The reticulum stain outlined the mast cells with a dense network of reticulum fibers (Fig. 80). Because of this intimate relation it is suggested that the mast cell may have a role in the formation of reticulum fibers.[13] The proximity of mast cells to the capillaries is nicely outlined by the reticulum fibers (Fig. 80). Masson's trichrome stain reveals a thinning of collagen fibers (Fig. 77), and probably accounts for the increase in reticulum. Special stains for elastic tissue showed a general absence of fibers throughout areas occupied by the mast cells (Fig. 81). Giemsa-stained touch smears or smears from the bullous forms of the disease reveal many mast cells usually containing the metachromatic granules (Fig. 82).

Electron microscopy of human cutaneous mast cells has recently been reported by Hibbs, Phillips and Burch,[10] and their findings are similar to ours. The type of mast cell most readily identified in the skin of our patients with systemic mastocytosis was a round or oval cell containing numerous granules. The granules in these cells are distinctive and generally arranged in a linear circular fashion about the nucleus. The granules are in close association with particulate material which appears as a lighter zone or halo. This particulate material assumes a spokelike pattern, and the amount present may vary from cell to cell. The cell membrane is osmiophilic with apparent aggregates of particulate material in close proximity (Fig. 83). The mast cell granules are most likely the site of synthesis of such material as sulfonated acid mucopolysaccharides (heparin), histamine and other organic compounds. There is a good possibility that the par-

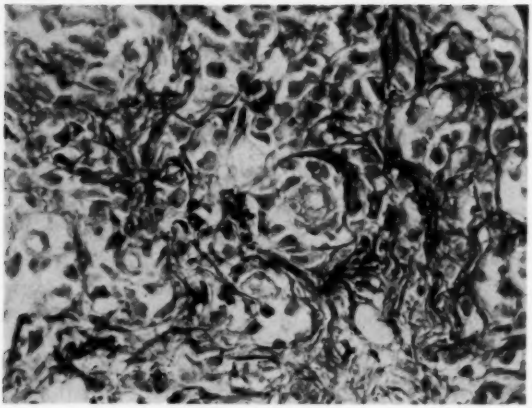

Fig. 81. Elastic tissue stain shows thinning or absence of elastic fibers. × 485.

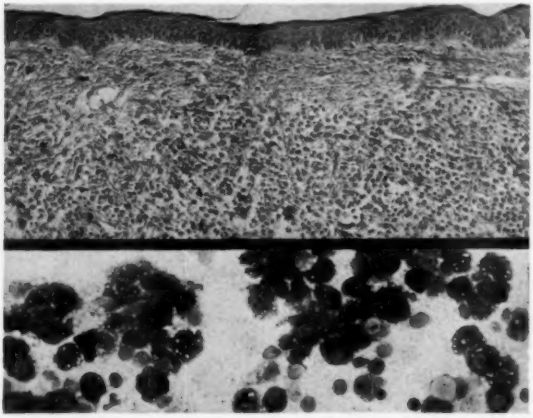

Fig. 82. Normal epidermis, Grenz zone and mast cell infiltrate (*top*). Touch smear from same area with Giemsa's stain, showing the mast cells (*bottom*). Composite magnifications, × 115 and × 300.

ticulate material viewed with the electron microscope represents some of the same compounds identified by histochemical techniques.

In the histologic differential diagnosis of mast cell disease, Sagher and Even-Paz[16] list some of the following diseases: Letterer-Siwe disease, eosinophilic granuloma, melanoma, juvenile xanthogranuloma (nevoxanthoendothelioma), leukemia, lymphosarcoma, reticulum cell sarcoma, and reaction to insect bite. According to Helwig,[11] other diagnoses such as intradermal nevus, lentigo and histiocytoma are also confused with mast cell disease. When cutaneous mast cell dis-

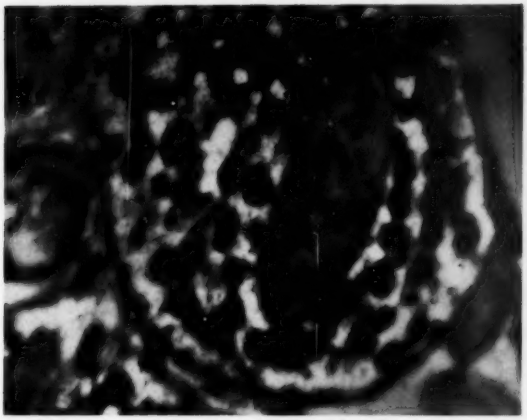

Fig. 83. Photomicrograph of mast cell as observed with an RCA EMU3C electron microscope. Linear arrangement of granules in association with particulate material. × 8000.

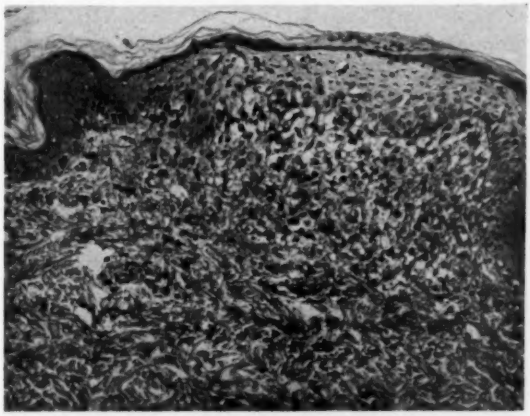

Fig. 84. Letterer-Siwe disease, showing papular elevation, parakeratosis, atrophy, liquefaction degeneration and infiltrate in the upper corium. × 135.

ease becomes vesicular or bullous, diseases such as dermatitis herpetiformis, erythema multiforme, contact dermatitis and other blistering eruptions must be considered. An excess of mast cells is not necessarily pathognomonic of mast cell disease. They may occur in large numbers in various chronic diseases, especially in chronic inflammation of the skin. Their presence is diagnostic only when they are found in large numbers and are the predominant cell, and when the appearance is correlated with the clinical picture. Most of the diseases listed above occur in children and will be discussed, citing the main distinguishing points from mast cell disease of the skin.

LETTERER-SIWE DISEASE AND EOSINOPHILIC GRANULOMA. Microscopic study under low-power objective reveals that the epidermis covers an irregular series of papular enlargements of the corium. There is usually parakeratosis, atrophy, and liquefaction degeneration of the basal layer (Fig. 84). Immediately beneath the epidermis the corium is comprised of loose, edematous tissue within which are numerous histiocytes, lymphocytes, dilated capillaries and extravasated red blood cells. The histiocytic cells contain a large round to ovoid nucleus with vacuolated clear cytoplasm, and these are the outstanding component (Fig. 85). The deeper corium is usually not altered, although it may be when eosinophils are present in great numbers, and then the microscopic features are more those of eosinophilic granuloma. Special stains do not demonstrate metachromatic granules or sulfonated acid mucopolysaccharides. Touch smears made from a cutaneous lesion of Letterer-Siwe disease and stained with either Giemsa's or Papanicolaou's technique reveal many large histiocytic cells with clear cytoplasm (Fig. 86). This is a useful, rapid method of separating Letterer-Siwe disease from mast cell disease.

JUVENILE XANTHOGRANULOMA (NEVOXANTHOENDOTHELIOMA). This disease commonly involves children and usually appears at birth or in the first two years of life. The lesions may be either single or multiple, and the nodules may be mistaken both clinically and microscopically for mast cell disease. This confusion has been referred to by Helwig,[11, 12] who up to the present time has studied material from 140 children with juvenile xanthogranuloma. Microscopic examination under the low-power objective usually reveals a slightly atrophic epidermis which is elevated over an ill-defined nodule which may extend

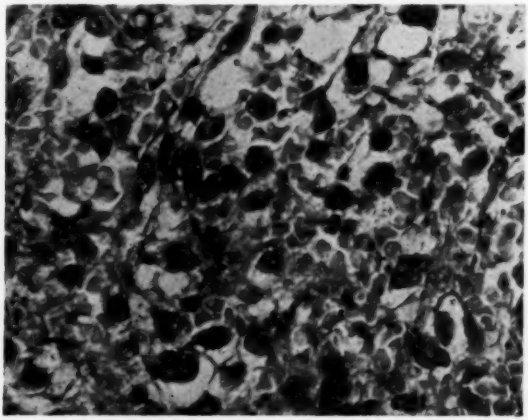

Fig. 85. Higher power of Figure 84 to show histiocytic cells, extravasated red blood cells and dilated capillaries. × 590.

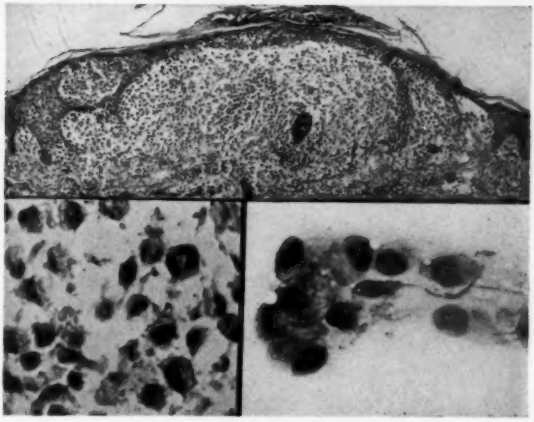

Fig. 86. Scanning and high-power field of Letterer-Siwe disease to show area from which a touch smear was made. The large histiocytic cells on the Giemsa-stained smear (*lower right*) are identical with those in the histologic sections. Composite magnifications, × 70, × 590 and × 590.

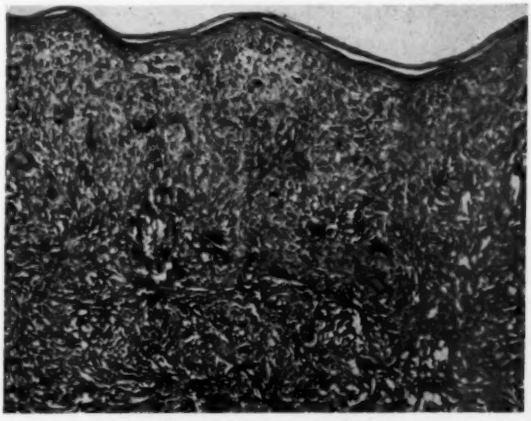

Fig. 87. Juvenile xanthogranuloma showing atrophic epidermis and ill-defined infiltrate in the corium. × 100.

into the upper subcutaneous tissue (Fig. 87). Under high-power examination the main features are those of many histiocytes, giant cells and fibroblastic cells distributed in an irregular pattern. There may be scattered foci of lymphocytes, plasma cells and eosinophils. Some histiocytes contain a foamy cytoplasm, and the giant cells are of the Touton type (Fig. 88). This latter feature is a positive differential point from mast cell disease. With special stains mast cells may be present, but the lack of large numbers and association with lipophagic histio-

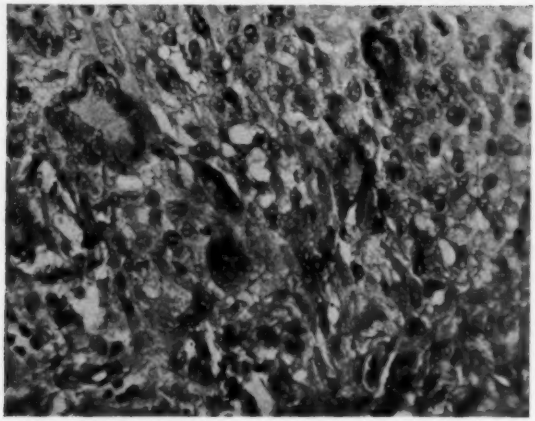

Fig. 88. Higher power of Figure 87 to show histiocytes, fibroblasts and Touton giant cells. Some histiocytes contain a foamy cytoplasm. × 400.

cytes and Touton giant cells distinguish the lesion as juvenile xanthogranuloma.

Malignant Lymphoma. A specific lymphomatous infiltrate in the skin of children is rare, but when it occurs it may be confused with mast cell disease. This is particularly true of leukemia cutis of the lymphatic type, although lymphosarcoma or reticulum cell sarcoma may cause confusion. Lymphatic leukemia, when examined under the low-power objective, usually reveals an essentially normal epidermis except for some flattening of the rete ridges. Immediately beneath the epidermis there is frequently a Grenz zone of uninvolved collagen. The remainder of the corium is occupied by masses of cells which may extend into the subcutaneous tissue. The infiltrate under high power is of one cell type, and these contain large hyperchromatic nuclei and frequently abnormal mitotic figures. The connective tissue stroma is thin and almost completely replaced by the infiltrate (Fig. 89). The monomorphous infiltrate seen in lymphocytic leukemia, lymphosarcoma and reticulum cell sarcoma is in contrast to the polymorphous infiltrate of mast cell disease. Special stains fail to demonstrate mast cells. A touch smear from a patient with lymphocytic leukemia cutis when stained by Papanicolaou's technique reveals numerous, large hyperchromatic cells which are all of the same type (Fig. 90). This is a rapid method of ruling out mast cell disease, but would be difficult to distinguish from Letterer-Siwe disease.

Insect Bite Reaction. The clinical aspects of insect bite reaction are discussed elsewhere (see p. 795). A recent publication by Mann and Bates[15] reviews the pathology of insect bites. At times some of

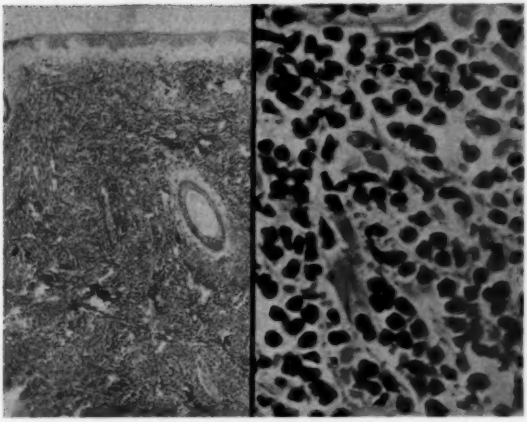

Fig. 89. Acute lymphatic leukemia with normal epidermis, Grenz zone, masses of lymphoblasts and thin connective tissue stroma. Composite magnifications, × 50 and × 485.

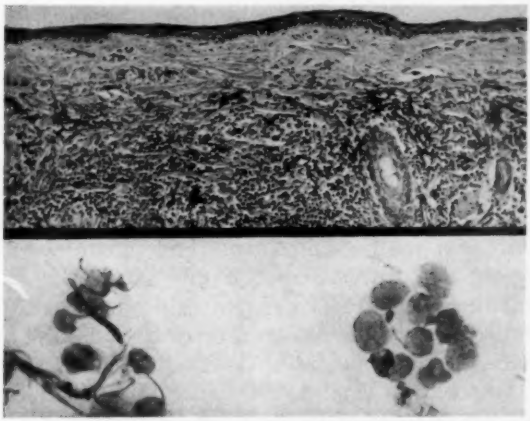

Fig. 90. Lymphocytic leukemia cutis (*top*) with touch smear (*bottom*) showing large cells all of the same type. Composite magnifications, × 115 and × 470.

the clinical and microscopic features are similar enough to lead to confusion with cutaneous mast cell disease.

The term "insect bite" is usually utilized in the literature to refer to any lesion caused by the classes Insecta and Arachnida of the phylum Arthropoda. Insect bite is a disease of fairly common occurrence in children and may be either acute or chronic. Allen[1] in 1948 focused the attention of the pathologist on chronic lesions of the skin following insect bites and pointed out that they were frequently confused with the malignant lymphomas. It has already been mentioned

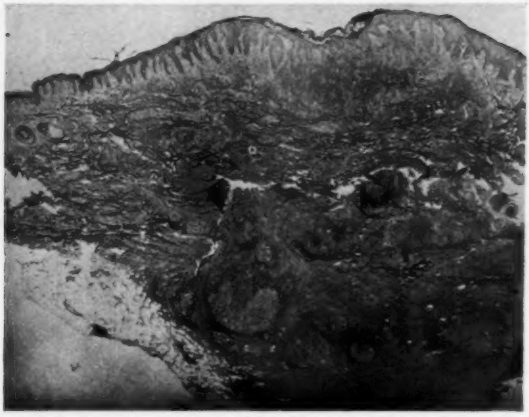

Fig. 91. Chronic insect bite reaction with depression of epidermis, acanthosis, and dense infiltrate involving corium and subcutaneous fat tissue. Lymphoid follicles are present. × 10

that this latter group can lead to confusion with cutaneous mast cell disease. A second type of insect bite reaction is a more acute allergic reaction, probably due to protein allergens, and this is often referred to as papular urticaria.

In chronic insect bite reaction the epidermis is raised over a diffuse and dense infiltrate in the corium. There is often a depression in an acanthotic epidermis which is filled with parakeratotic material, and at the base there may be pseudoepitheliomatous hyperplasia extending into the upper and middle corium. The infiltrate extends from the epidermis into the deep corium and subcutaneous fat. In different fields the infiltrate may be of different density and pattern. Most of the connective tissue of the corium is obscured and finely separated by the infiltrate (Fig. 91). High-power examination reveals a polymorphous infiltrate composed of lymphocytes, histiocytes, reticular cells, plasma cells and scattered eosinophils. At times the pattern may be that of numerous lymphoid follicles with germinal centers in which there are large reticular cells with pale nuclei, and some contain mitotic figures (Fig. 92). If the marginal area is viewed, the cells appear small and of one cell type, and it is these features that tend to mimic malignant lymphoma. The capillaries may at times show endothelial swelling and perivascular fibroblastic proliferation accompanied by edema and infiltration of the wall with inflammatory cells. There may be collections of inflammatory cells including polymorphonuclear leukocytes which are aggregated about areas of necrosis. Identification of remnants of the insect (Arthropod) with foreign body giant cell reaction is diagnostic. If a Giemsa's stain is done, there may be numerous mast

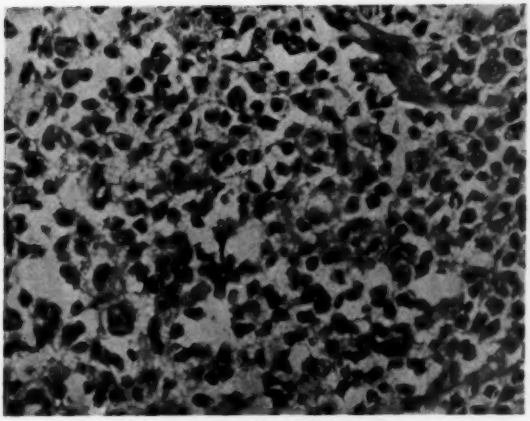

Fig. 92. Higher power of Figure 91, showing germinal center with large reticular cells. × 400.

cells present, but when all the features are considered such as epidermal changes, pattern and the type of inflammatory infiltrate, a diagnosis of chronic insect bite can be favored over mast cell disease or malignant lymphoma.

In papular urticaria there are fairly definite histologic criteria for making the diagnosis. The early urticarial phase is histologically similar to ordinary acute insect bites and consists of edema and a perivascular and periappendageal inflammatory infiltrate in the middle and lower dermis. The infiltrate is composed of lymphocytes, histiocytes and eosinophils. In the persistent or papular type there is an inflammatory infiltrate located about the capillaries of the mid and lower dermis. This is composed of eosinophils, polymorphonuclear leukocytes, and histiocytes. An occasional lesion may show a focus of necrosis. There is usually endothelial swelling and thickening of the vessel walls, and some are occupied by the inflammatory infiltrate. These latter features suggest an allergic angiitis or antigen-antibody type of vascular insult (Fig. 93). Some types show only a cellular infiltrate composed primarily of lymphocytes. Giemsa's stain may reveal mast cells, but they are not the predominant cell, and this along with a mixed infiltrate, necrosis and angiitis, favors the diagnosis of papular urticaria.

Nevi and Melanoma. In children these lesions appear the same as in adulthood with the exception of two special forms referred to as spindle cell and epithelioid cell nevi. These types are seen predominantly in children, but may also occur in adults. Microscopic confusion of some types of junction, compound or intradermal cellular nevi with mast cell disease may occur.

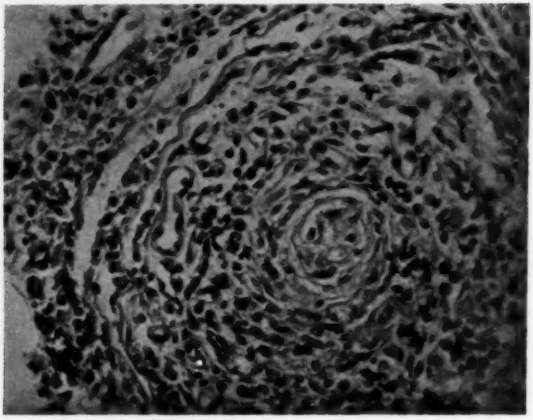

Fig. 93. Papular urticaria showing angiitis of vessels. There is endothelial swelling and thickening of the vessel wall occupied by acute inflammatory cells. × 300.

Junction cellular nevus in children would only rarely be confused with mast cell disease. One circumstance is the so-called halo nevus or leukoderma acquisitum centrifigum in which there is loss of pigment in and about the nevus. Microscopic features are those of a junction nevus that is hard to recognize because of lack of pigment in the nevus cells and a dense inflammatory infiltrate hugging and invading the epidermis. This combination of factors makes some of the nevus cells, lymphocytes or histiocytes appear as mast cells, but index of suspicion for the lesion, histochemistry, and correlation with the clinical features are the distinguishing points. A two-year old Negro child with multiple halo nevi has recently been studied in our institution. The DOPA technique was used on fresh biopsy tissue from two lesions, and indicates an active tyrosine-tyrosinase enzyme system in the nevus cells. There is a good possibility that the melanin being produced is rapidly released from the nevus cells and immediately carried off by the lymphatics.

Histologic examination of intradermal cellular nevus shows nests and strands of nevus cells located only in the dermis. There is no junction activity, and usually a definite Grenz zone of normal collagen separates the epidermis from the nevus cells. The cells are uniform and cohesive, and contain an ovoid or round basophilic nucleus and a slightly eosinophilic granular cytoplasm. Nevus giant cells may be present, and the amount of melanin pigment is variable (Fig. 94). The presence of nevus giant cells and melanin pigment, and absence of eosinophils and metachromatic granules would rule against mast cell disease.

Compound spindle and epithelioid cell nevi are referred to by

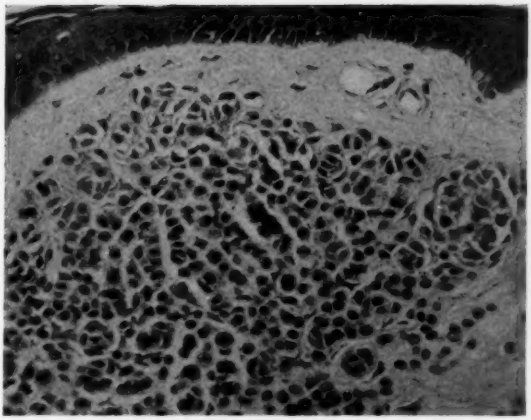

Fig. 94. Intradermal cellular nevus with no junction activity, Grenz zone, nevus cells, giant cells and melanin pigment. × 300.

Allen[2] as juvenile melanomas. The terms "spindle cell nevus" and "epithelioid cell nevus," as used by Helwig[11] and Kernen and Ackerman,[14] are preferred for these lesions in children (juvenile nevus) because of the possibility of confusion with malignant melanoma. They are benign lesions and should not be called melanoma. Microscopic study of spindle cell nevus usually reveals a dome-shaped elevation of the epidermis which is acanthotic and at times approaches pseudoepitheliomatous hyperplasia. There are nests of spindle-shaped nevus cells between and sometimes surrounded by elongated and intercommunicating rete ridges of the epidermis. Nests and strands of these nevus cells extend into the dermis and sometimes as deep as the subcutaneous fat tissue. There is usually only a scant connective tissue stroma with dilated capillaries separating the nevus cells. The nevus cells tend to group into short sweeps of parallel cells in irregular arrangement, but more or less perpendicular to the epidermis (Fig. 95). The cells are large and spindle-shaped, with light basophilic staining oval or elongated nucleus and acidophilic cytoplasm. The cells are cohesive and show good relationship to each other and the surrounding stroma (Fig. 96). Mitotic figures may be present. Melanin pigment may be slight in amount, but at times is abundant. The base of the lesion is usually ill-defined. Inflammation is absent or only slight unless there is ulceration of the epidermis. In some lesions there are areas where the cells take on an epithelioid appearance, and rarely all the cells are of this type (Fig. 96). When this occurs, the lesion may be called an epithelioid cell nevus. The distinguishing features of these two lesions from mast cell disease would be the presence of nevus cells at the epidermal-dermal junction which extend into the corium

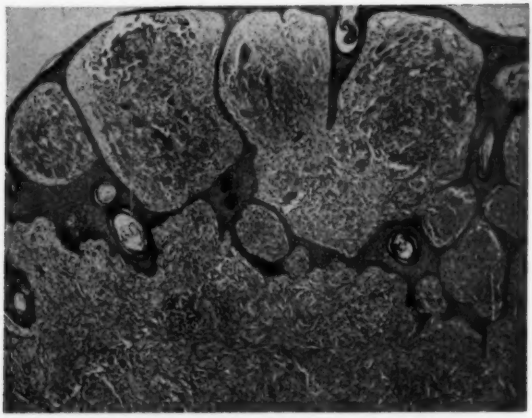

Fig. 95. Compound spindle cell nevus, which is elevated, shows junction activity, pseudoepitheliomatous hyperplasia and irregularly arranged sweeps of spindle cells. × 50.

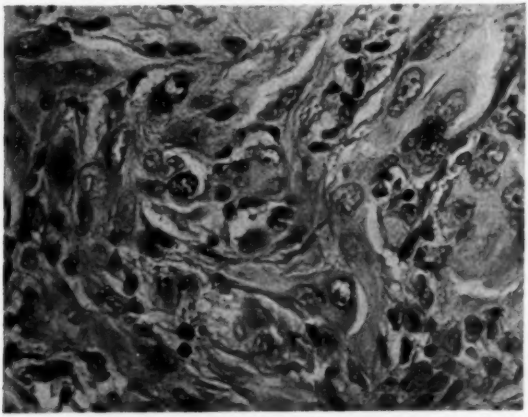

Fig. 96. High-power field of a juvenile nevus showing both spindle and epithelioid types of cells. The cells are uniform and cohesive. × 15.

in the form of nests and strands. The presence of melanin pigment and absence of metachromatic granules with Giemsa's stain would also be distinguishing points. Histochemical studies utilizing acid mucopolysaccharide (AMP) and alcian blue techniques reveal positive material in the cytoplasm of nevus cells. The aldehyde-fuchsin reaction is negative, indicating that the material is not a sulfonated acid mucopolysaccharide. This is of definite aid in distinguishing nevus cells from mast cells.

When malignant melanoma occurs in children, the same features

Fig. 97. Elevated lesion of malignant melanoma with cells located at the epidermal-dermal junction and invading the corium. × 13.

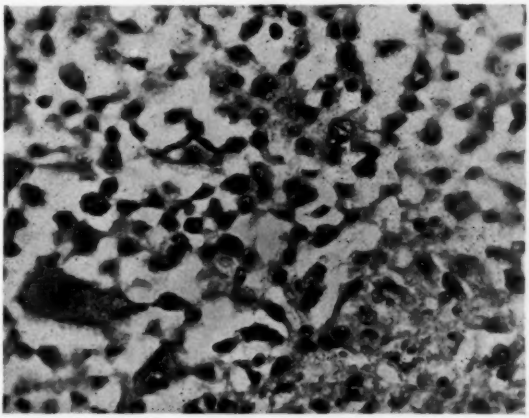

Fig. 98. Higher power of Figure 97 showing pleomorphic melanoma cells. The nuclei are hyperchromatic and bizarre, and contain prominent nucleoli. Mitotic figures, melanin and multinucleated cells are present. There is loss of cohesion and poor relation to the surrounding stroma. × 415.

are present as in adults and there is a similar biologic potential for metastasis. This latter tendency is not the natural history of a spindle or epithelioid cell nevus of childhood. The microscopic features of melanoma are those of an elevated lesion with pleomorphic melanoma cells located at the epidermal-dermal junction and invading the dermis (Fig. 97). The cell membranes are poorly defined, and there is variation in size, shape and nuclear staining. The nuclei are hyperchromatic and bizarre, and contain prominent nucleoli, and some cells are

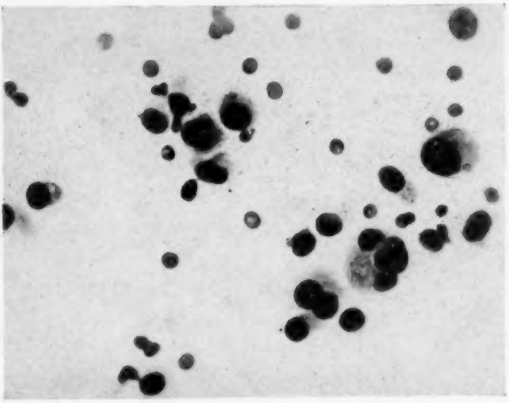

Fig. 99. Touch smear of malignant melanoma showing hyperchromatic nuclei, bizarre cells and multinucleated forms. × 500.

multinucleated. Mitotic features may be present in great numbers, and these are often abnormal. The cytoplasm usually contains an abundance of fine melanin granules. Melanoma cells usually show loss of cohesion for each other, and there is poor relationship to the surrounding stroma (Fig. 98). Although mast cell disease has been confused with malignant melanoma, the presence of pleomorphic melanoma cells at the epidermal-dermal junction, melanin, and mitotic figures are the main distinguishing features. Histochemical reactions of melanoma cells are the same as described for spindle and epithelioid cell nevi. Touch smears made from malignant melanoma and stained by Papanicolaou's technique reveal large pleomorphic cells with abnormal nuclear cytoplasmic ratio, bizarre hyperchromatic nuclei, prominent nucleoli and multinucleated forms (Fig. 99). This procedure is a rapid method of differentiating malignant melanoma from benign nevi and mast cell disease in children. Loss of cohesion and relationship to the surrounding tissue stroma probably account for the large number of cells present on touch smears.

Lupus Erythematosus and Polymorphic Light Eruption

Lupus erythematosus is the subject of another of the papers making up this symposium (see p. 873). Again the clinical and microscopic features are similar enough to cause confusion. The pathology of these two diseases has recently been discussed by Wright and Winer.[20]

Lupus Erythematosus. Microscopic sections usually show hyperkeratosis, follicular plugging, accentuated granular layer, atrophy and

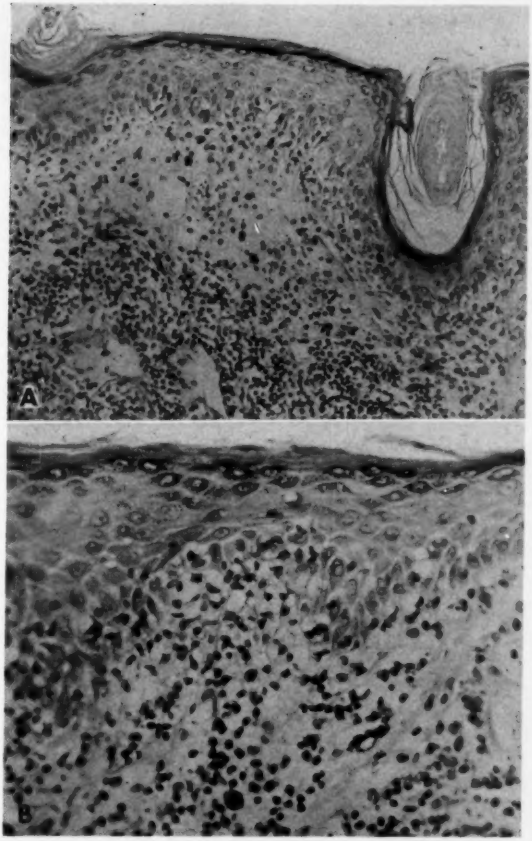

Fig. 100. A, Lupus erythematosus showing follicular hyperkeratosis, atrophy, dermal infiltrate, edema and vascular ectasia. There is atrophy of the pilosebaceous follicle. × 165. *B*, Lupus erythematosus showing accentuated granular layer, liquefaction degeneration, melanin pigment, edema and infiltrate. × 300.

liquefaction degeneration of the basal layer of the epidermis. Parakeratosis is usually not present, but when seen does not rule out the diagnosis. In the upper corium there is interstitial edema, vascular ectasia and melanin pigment which is both lying free and located in melanophages. A constant feature is the presence of inflammation about adnexal structures and capillaries and composed predominantly of lymphocytes and histiocytes. There is usually evidence of atrophy of the pilosebaceous follicle (Fig. 100).

POLYMORPHIC LIGHT ERUPTION. The microscopic features of this disease may closely mimic those of lupus erythematosus, and the dis-

ease is at times extremely difficult to differentiate on the basis of histologic changes. Polymorphic light eruption usually shows hyperkeratosis, parakeratosis, slight acanthosis, intact granular layer and spotted liquefaction degeneration of the basal layer of the epidermis. In the corium there is edema, vascular ectasia, and a prominent perivascular infiltrate made up predominantly of lymphocytes and histiocytes, although occasional eosinophils and polymorphonuclear leukocytes are seen (Fig. 101). The pilosebaceous follicle is usually intact, but follicular plugging does not rule against the diagnosis. Overlapping of histologic features occurs, but the combination of hyperkeratosis, parakera-

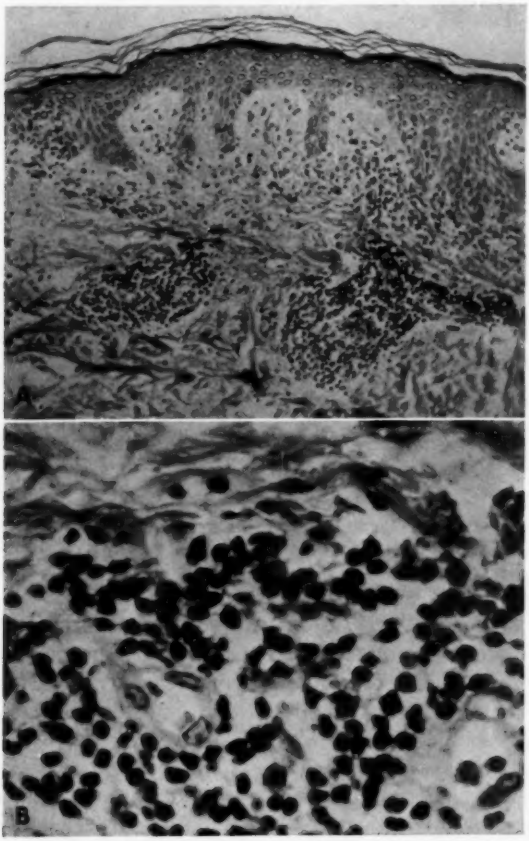

Fig. 101. A, Polymorphic light eruption showing slight hyperkeratosis, intact granular layer, mild acanthosis, spotted liquefaction degeneration of the basal layer, edema in the upper corium, and a perivascular infiltrate. × 135. *B*, Higher power showing a vasculitis and infiltrate of lymphocytes and histiocytes. × 700.

tosis, spotted liquefaction degeneration and a vasculitis favors the diagnosis of polymorphic light eruption. There is a possibility that the two may be related or different phases of the same disease process.

Pilomatrixoma

Pilomatrixoma has been reported in adults by Forbis and Helwig.[7] In collaboration with Bingul and Helwig[8] a detailed clinicopathologic analysis of 84 children with pilomatrixoma (benign calcifying epithelioma of Malherbe) was undertaken. The tumors are generally single, as verified by the presence of 92 tumors in 84 children. Four patients had two tumors each, and one had four tumors. The median age was 6.5 years at the time of excision. The youngest patient was 8 months of age, and the oldest was 14 years. The average duration from onset to removal was 2.2 years, and the median 1.8 years. Two of the tumors were reported to have been present at birth. The tumors occurred predominantly in the Caucasian race and more often in females. The lesions also occurred in two Negro patients and in one Oriental. Anatomically, the lesions were located on the face, upper extremities, neck, shoulders, back, chest, lower extremities, and scalp. The lesion has a predilection for the face, neck and arms. The palms and soles were not involved. Clinically, the tumor was a subcutaneous nodule with a median size of 1 cm. A few patients reported bluish or reddish discolorations and recurrent episodes of inflammation.

About 30 per cent of the patients from whom follow-up data were available experienced pain, usually on pressure. The initial clinical diagnosis was most frequently a cyst or sebaceous cyst. The diagnosis of pilomatrixoma was not suspected in a single instance. Follow-up data were obtained from 52 patients for a median period of 7 years. Pilomatrixoma appears to be neither hereditary nor familial and is not influenced by geographic location. There is no evidence of associated systemic disease. The natural history is that of a benign tumor. Surgical excision of the lesion was the treatment of choice.

The initial histopathologic diagnosis was most frequently benign calcifying epithelioma of Malherbe, followed by epidermoid cyst. Five lesions were initially diagnosed as malignant processes. Microscopic examination of the lesion revealed a normal or compressed epidermis except in rare instances (2 to 3 per cent) in which there was a dilated follicular crypt opening onto the skin surface. The main feature was a circumscribed mass located in the dermis and frequently in the subcutantous fat tissue (Fig. 102). The tumor was surrounded by compressed collagen and was composed of bands and sheets of epithelial cells. These were often folded or convoluted and separated by a connective tissue stroma. Occasionally smaller masses of epithelial cells

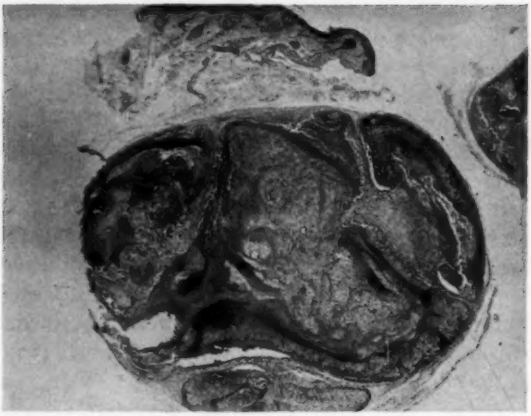

Fig. 102. Pilomatrixoma appearing as a circumscribed tumor in the dermis and subcutaneous fat. × 15.

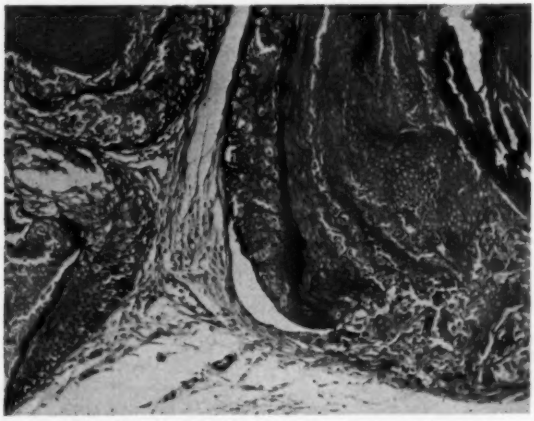

Fig. 103. Higher power of Figure 102 showing basophilic cells, hyalinized cells, shadow cells and calcium deposit. × 115.

were arranged in a circular configuration. The stem or matrix epithelial cell contained a basophilic staining nucleus, finely divided nuclear chromatin, small nucleolus and a scanty, pale eosinophilic cytoplasm. The cell boundary was ill-defined or not visible. These basophilic cells occurred in solid masses and had a high mitotic activity. Four different fates of the basophilic cells were present: transition to shadow cells, hyalinized shadow cells, squamoid cells and degenerated cells (Fig. 103). Some squamoid-like cells had intercellular bridges and contained a hyalin material resembling trichohyalin of

the pilar inner root sheath. There was no evidence of changes to suggest a malignant transition in any of the lesions studied. Keratin could be found in some areas along with amorphous debris and red blood cells. A foreign body type of reaction with numerous giant cells, lymphocytes, histiocytes and polymorphonuclear leukocytes was a constant finding. Many spaces engorged with red blood cells were present. These spaces were not lined by endothelium and ended blindly, but some showed communication between the tumor cells and stroma. This latter feature probably accounts for hemosiderin deposits in 20 per cent of the tumors. Melanin was rarely (2 per cent) noted in the shadow cells. Calcification (Fig. 103) and ossification were observed in 90 and 10 per cent of the tumors, respectively. Definitive similarities have been found between pilomatrixoma and hair. It is generally accepted that the tumor arises from primitive epidermal germ cells which are differentiating toward hair matrix cells. Perhaps the origin may be in the migration of a primitive cell from the epidermis downward. This is suggested by the presence of some tumors which connect with the epidermis in a follicle-like opening.

SUMMARY AND CONCLUSIONS

In the first phase of this report the remarks are not new or original. The discussion has pointed up well established principles and procedures practiced and adhered to by all who have the responsibility of making diagnoses from histopathologic sections. The biopsy is a combined effort on the part of the clinician, technician and pathologist. For the best possible results it requires close collaboration of both clinician and pathologist. The objective is directed toward the establishment of a correct diagnosis that will aid in the handling of the patient involved. It is the responsibility of the general pathologist or dermal pathologist to have a good working knowledge of clinical dermatology so as to evalute properly the specimens he is studying.

It is ill-advised for every dermatologist, though he be an expert in morphology, to consider himself a dermal pathologist. Likewise, those in general pathology, even though experts in evaluating other organ systems, should make a special effort to gain insight into and knowledge of the skin before glibly signing out a specimen as chronic dermatitis. Dermal pathology might be considered a specialty within the specialties of pathology and dermatology, and rightly belongs to those with training and knowledge in these fields.

The role of the dermal pathologist is cited and values are pointed out in the discussion of specific diseases. A detailed clinicopathologic analysis of 84 children with pilomatrixoma is presented.

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THE STRUCTURE AND FUNCTION OF THE EPIDERMIS

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The reader may believe that it is unnecessary or absolutely useless to discuss the development, structure and function of normal epidermis in an article directed primarily at physicians who are pediatricians or general practitioners. We believe, on the other hand, that a thorough understanding of the modern disciplines of biology, anatomy and biochemistry of the skin, during its different phases of development, will enhance our understanding of the appearance, development and regression of certain cutaneous afflictions in the child or in the adult. By keeping in mind the fundamental properties of skin, we may in time come to understand the subtle and often elusive differences that exist in the physiology and in the pathologic manifestations of the skin of the child, that of the young and mature adult, and that of the aged.

Thus, for example, the skin of the child has a thinner epidermis, and particularly the stratum corneum and the transitional layer, than that of the adult. It has relatively undeveloped and poorly functional sebaceous and apocrine sudoriferous glands. Differences in activity between immature and adult skin necessarily follow, both in the more generalized processes of inflammation and keratinization, and the more localized responses of sudoriferous and seborrheic elements.

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Supported in part by Grant RG-6068(C2) of the National Institutes of Health, U.S. Public Health Service (Massachusetts Memorial Hospitals), and in part by Grant RG-2125(C11) of the National Institutes of Health, U.S. Public Health Service (Brown University).

The epidermis is indubitably the most important cutaneous structure, having as its major function the production of keratin and melanin. As the outer layer of the body, it is interposed between the changing external world and the vital organs, to which it must communicate the changes which take place. At the same time the epidermis must also reflect, often in subclinical ways, alterations that take place in the organs of the body by varying its cellular metabolism. During recent years a rich enzymatic patrimony has been demonstrated in the epidermis; such a patrimony is not identical in the embryo, the child, and the adult.

Even though, for many years, the connective tissues of the dermis have been given justly deserved prominence as vital to the economy of the organism, the epidermis remains, for the dermatologist, the noble structure, the integrity of which is absolutely indispensable to the proper function of the rest of the skin. A knowledge of its morphology and function can only profit those who must know how to interpret its pathologic manifestations. In this short article we shall begin by giving a brief review of its development, mentioning some of the most recent findings and bringing to light some of the knowledge which we now are obtaining on the biology of the skin of the fetus and the child.

THE EPIDERMIS OF THE FETUS

The epidermis arises from the general surface ectoderm. From the epidermis later develop the sudoriferous glands, the pilosebaceous complexes and the nails. The dermis and the hypodermis develop from the mesenchymatous mesodermal envelope. Early in the differentiation of the embryonic skin the primitive epidermis is invaded by a second type of cell from the neural crest, which gives rise to the pigmentary system, the melanocytes.

About the third week of fetal life the epidermis consists of a single layer of undifferentiated cells (Fig. 104); in the fourth week it becomes two-layered. The outer layer, the *periderm* or *epitrichial* layer, has a protective function, and the basal layer, the *stratum germinativum* or *basale*, is the parent tissue of all subsequent cutaneous structures. The germinative layer, beginning between the tenth and twelfth fetal weeks, proliferates in a centrifugal direction to form a *stratum intermedium* (Figs. 105,106); by about the sixteenth fetal week this becomes stratified, forming a spinous layer. The germinative layer proliferates also in a centripetal direction, giving rise to clusters of cells that grow into the subjacent dermis; these differentiate into epidermal ridges proper and the adnexa, the pilosebaceous complexes and the sudoriferous glands, which begin to differentiate from the tenth to the fourteenth fetal weeks and continue thereafter (Figs. 106,

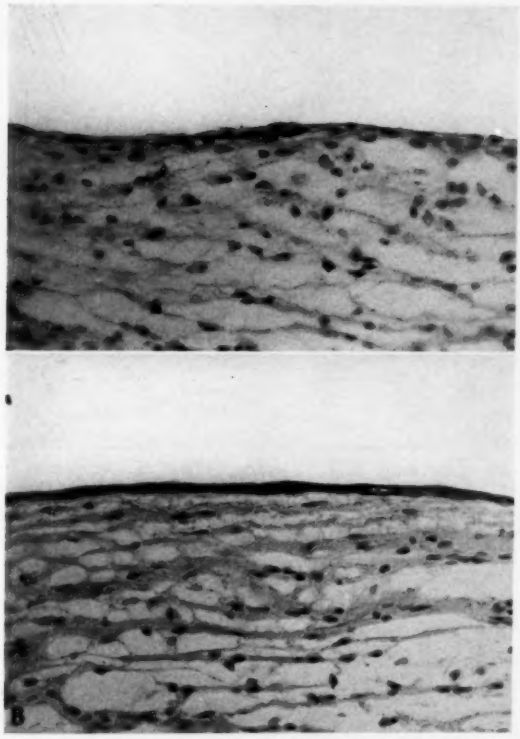

Fig. 104. Skin of the abdomen in a 4-weeks-old fetus. *A*, The periderm alone is well visualized. In occasional areas the germinative layer appears to be developing. Hematoxylin-eosin. × 800. *B*, Illustrating the presence of glycogen throughout the epidermis. Periodic acid Schiff. × 800.

107). Between the ninth and the twelfth weeks an invagination of the epidermis on the dorsal surface of the finger tips first establishes the posterior limiting sulcus and the matrix of the nail bed.

From about the seventeenth week onward the periderm gradually disappears and is replaced by a stratum corneum. This layer slowly attains thickness and compactness, achieving at term the characteristic features of the postnatal stratum corneum. The development of the epidermis is dischronous in the various regions of the body. Differentiation takes place first in the lips, nose and eyebrows, where changes are evident from the tenth to the thirteenth weeks. It is slower on the back, the abdomen and the limbs.

The structure and function of the cells of the periderm must be influenced by the amniotic fluid which bathes this layer and by which its metabolism is presumably conditioned. Peridermal cells are largely

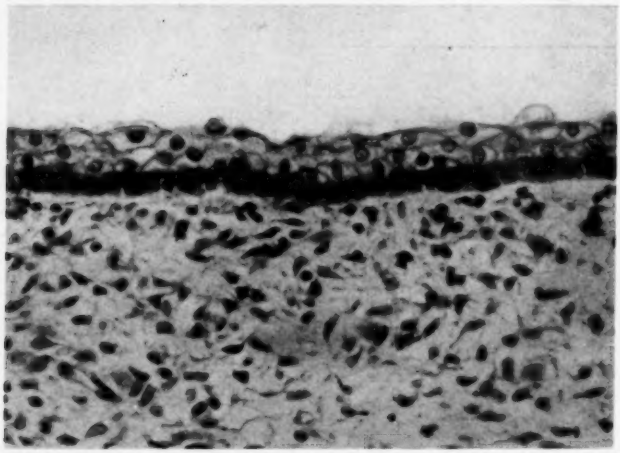

Fig. 105. Skin of the hand in an 11-weeks-old fetus. The epidermis is composed of clearly defined cuboidal basal cells and 2 or 3 layers of cells of the periderm. The stratum intermedium is beginning to appear immediately above the basal layer. Toluidine blue. × 800.

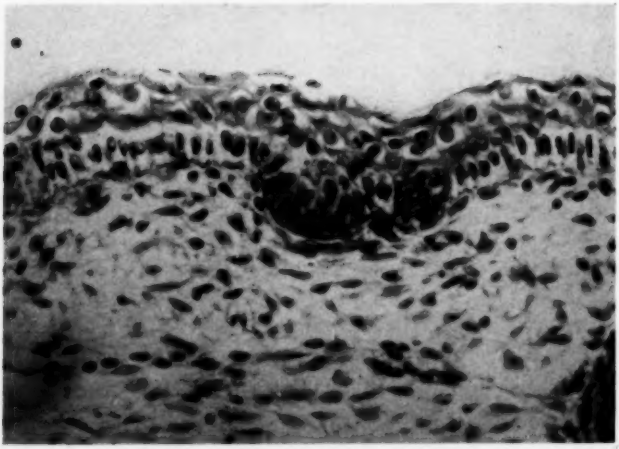

Fig. 106. Skin of the face in a 16-weeks-old fetus. The cells of the basal layer are columnar, and the intermediate cells are abundant and well visualized, as are the cells of the periderm. Note developing primary and secondary hair germs and basement membrane. Toluidine blue. × 800.

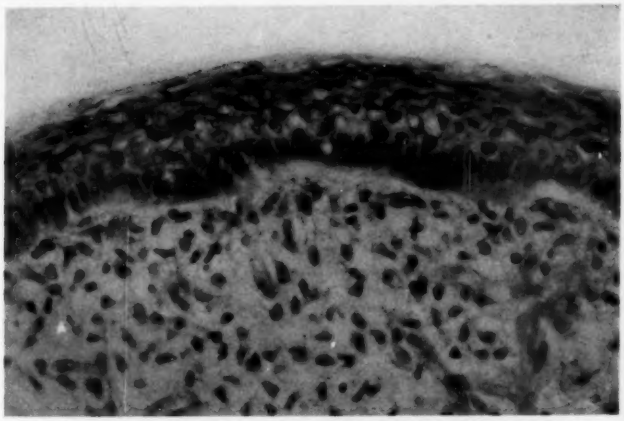

Fig. 107. Skin of the finger in an 11-weeks-old fetus. The epidermis consists of basal, intermediate and epitrichial layers. The epitrichial layer is formed by numerous layers of flattened cells. At 2 sites of the basal layer is seen early aggregation of cells with hyperchromatic nuclei, indicating the early stage of the development of rete ridges from which will later arise the sweat glands. Toluidine blue. × 800.

flattened, polygonal and polymorphic, with oval nuclei and vacuolated cytoplasm (Figs. 104, *A*; 105). At first one-cell thick, the periderm later becomes stratified. The surface cells in contact with the amniotic fluid often form globular masses that seem to be detached from the subjacent cells and probably escape into the amniotic fluid (Fig. 108, *A*). The peridermal cells contain some mucopolysaccharides and are replete with glycogen and lipids, although these substances gradually diminish as the subjacent epidermis attains its characteristic postnatal structure (Figs. 108, *B*; 109). These cytoplasmic polysaccharides, which are found in the peridermal cells during early fetal life, are probably synthesized from carbohydrates derived from the amniotic fluid, which is known to contain about 30 mg. per 100 ml. of glucose.

There is controversy about the fate of the cells of the periderm. Some believe that they become modified into a stratum granulosum and a stratum corneum, but there is no valid basis for this assumption. It seems to us that the major function of the periderm is protection; it disappears after the fourth or fifth fetal month, being replaced by the stratum granulosum and the stratum corneum, and, in the friction areas, the stratum lucidum. Histochemical investigations of the development of the skin of the rat[7] and that of man[10] support our view that the periderm is shed at the same rate that it is replaced by the stratum corneum. Let us emphasize that even during the last phases of intrauterine life, the newly formed stratum corneum is not in direct contact with the amniotic fluid, being covered by the *vernix caseosa*,

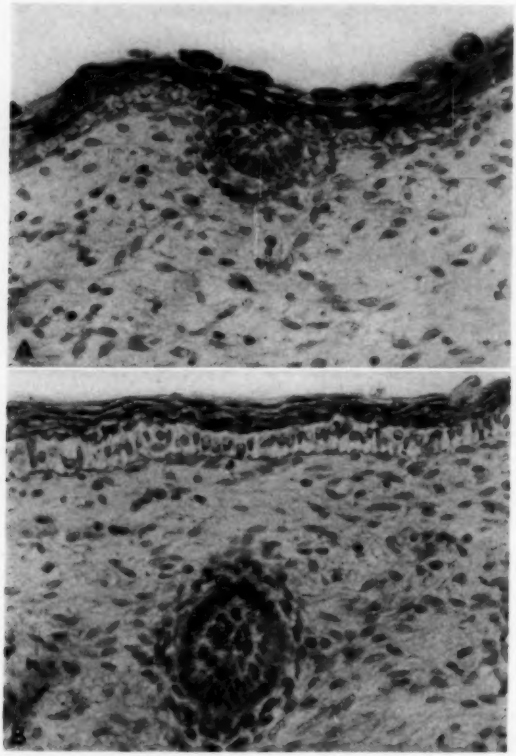

Fig. 108. Skin of the scalp in a 16-weeks-old fetus. A, The periderm and the intermediate layer are loaded with glycogen, which is relatively absent from the basal cells. The periderm cells are polymorphous, but tend to be globular and to become detached at the surface. Periodic acid Schiff. × 800. B, Glycogen is abundant in the cells of the periderm and intermediate layer, but is totally absent from the columnar basal cells. Periodic acid Schiff. × 800.

a complex mixture of sebum, residues of peridermal cells, shed lanugo hairs and probably other debris.

The embryonic germinative cells are large and have a distinct nucleus. In early embryos they are cuboidal; later the cells become cylindrical, and the nucleus, located in the distal portion of the cell, stains intensely. From the thirteenth to the sixteenth fetal weeks centrifugal proliferation gives rise to a stratum intermedium, first in the perioral and perinasal regions of the face. The cells of the new layer are somewhat oval and smaller than those of the basal layer. Soon after it is first formed, the stratum intermedium becomes layered and stainable cytoplasmic fibrils appear in its cells. The stratum intermedium, then, is the stratum spinosum.

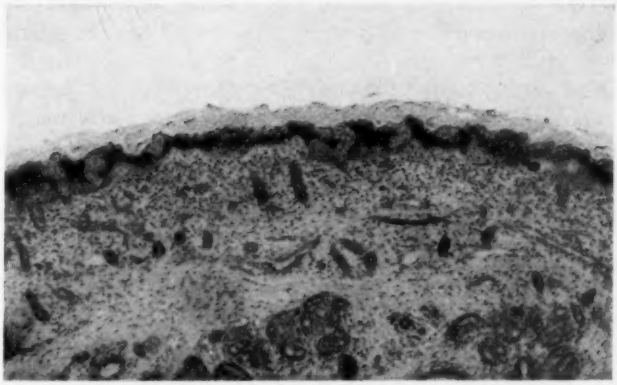

Fig. 109. Skin of the sole in a 26-weeks-old fetus. The normal layers of the epidermis are now well developed. The horny layer is thick, and almost all the cells of the rete ridges are still rich in glycogen. Periodic acid Schiff. × 140.

From ten to fourteen weeks, crests and concavities develop on the under side of the epidermis and fit into the concavities and crests of the subjacent dermis.

During the second period of fetal life adjacent epidermal cells are in contact with each other by means of small cytoplasmic projections called intercellular bridges. A swelling midway to each intercellular bridge is the point of contact of two adjacent cell membranes; these are the desmosomes or nodes of Bizzozero The dermoepidermal junction, indistinct during early fetal life, later assumes the characteristic feature of a basement membrane.

Beginning in the third fetal month, numerous nerve terminals from the subepidermal nerve arcades penetrate the epidermis (Fig. 114). These intraepidermal nerves, numerous in the early fetal months, appear to be spaced farther apart during the later stages of gestation, perhaps as a result of dilution by the growth of the surface area.[11]

Several histochemically demonstrable enzymes have been found even in the epidermis of embryos eight to ten weeks old. Amylophosphorylase, succinic dehydrogenase, cytochrome oxidase, phosphatases and various esterases show good reactions. These and other enzymes, indistinct during early fetal life, become increasingly active during the subsequent epochs of development.[10]

As long as the cells of the periderm have a stainable nucleus, the subjacent epidermal cells contain no keratohyalin granules. Keratohyalin granules first make an appearance in the cells high up in the spinous layer near the end of the fifth fetal month, in places where the epidermis is thicker, such as the perioral, perinasal and periocular regions, and particularly around the orifices of the pilary canals. Over

most of the general body surface the stratum granulosum develops later. Keratinization seems to progress only after a stratum granulosum has developed. With the beginning of keratinization, there is an increase in demonstrable -SH and -S-S- groups in the upper layers of the epidermis, and glycogen largely disappears, only traces of it remaining in the upper layers of the stratum spinosum.

THE STRUCTURE OF THE EPIDERMIS OF THE INFANT AND OF THE ADULT

The epidermis is a stratified epithelium composed of cells of different form, size, composition and viability. The number of layers of cells varies from one region of the body to another, and according to the age, sex and physical makeup of the person. The epidermis is composed of a *basal* or *germinative layer*, above which is a *stratum spinosum* or true *mucous layer* of Malpighi, a *stratum granulosum* and a *stratum corneum* at the surface (Figs. 110, 111, 112). Where the epidermis is thickest, as in the palms and soles, a hyalin layer, the stratum lucidum of the Italian anatomist Oehl, is interposed between the stratum granulosum and the stratum corneum.

The *stratum basale*, or *germinativum*, consists of a single layer of cylindrical cells, the basal portion of which is in contact with the dermis (Fig. 112, A). The columnar or cuboidal cells have a relatively large, oval nucleus which stains intensely with basic dyes. Depending

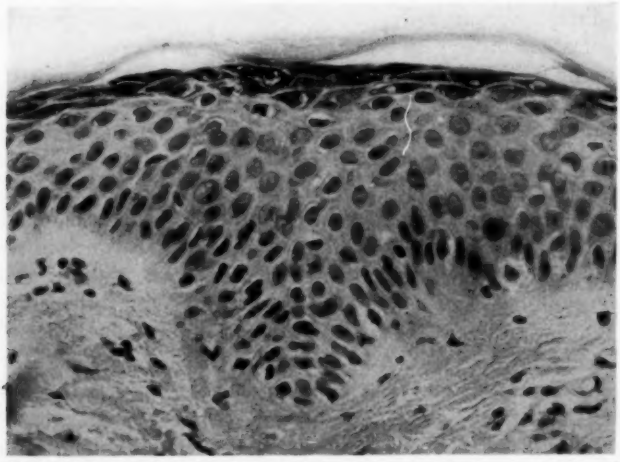

Fig. 110. Skin from the face of a middle-aged man. The layers of the epidermis are well illustrated in the area of this rete ridge: the columnar cells of the basal layer, the prickle cell layer, the granular layer and the horny layer. Note at the extreme right a "clear cell" in the basal layer. Hematoxylin-eosin. × 800.

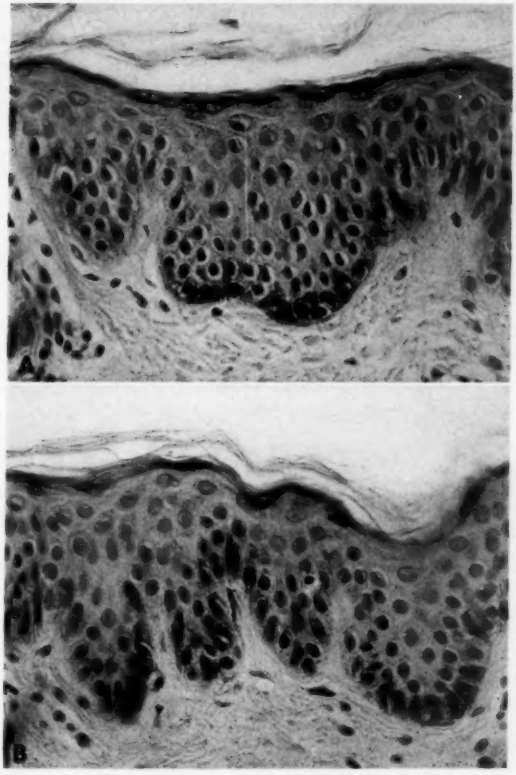

Fig. 111. Skin of the face of a man. *A*, The cells of the basal layer are moderately pigmented. There is some widening and thickening of a rete ridge. Here and there may be noted vacuolated cells in the malpighian layer and nucleated cells in the horny layer. Hematoxylin-eosin. × 800. *B*, Abundant pigment is present in the basal layer, and there is a "clear cell" in the center. There is mild parakeratosis and a relative absence of the granular layer. Hematoxylin-eosin. × 800.

upon the size of the cell, the nucleus may occupy the greater portion of the cell, or it may be shifted somewhat toward the base. The germinative cells are anchored to the superficial dermis by way of delicate, cytoplasmic processes which are difficult to demonstrate in ordinary histologic sections. The processes can be seen in very thin sections of well fixed material or, better, in frozen sections viewed under the phase contrast microscope. In preparations stained with iron hematoxylin, or treated with silver impregnation, the flexuous, corkscrew-like structures, the filaments of Herxheimer, can be seen arranged perpendicular to the surface, apparently occupying the basal cytoplasmic processes of the germinative cells. Various authors have

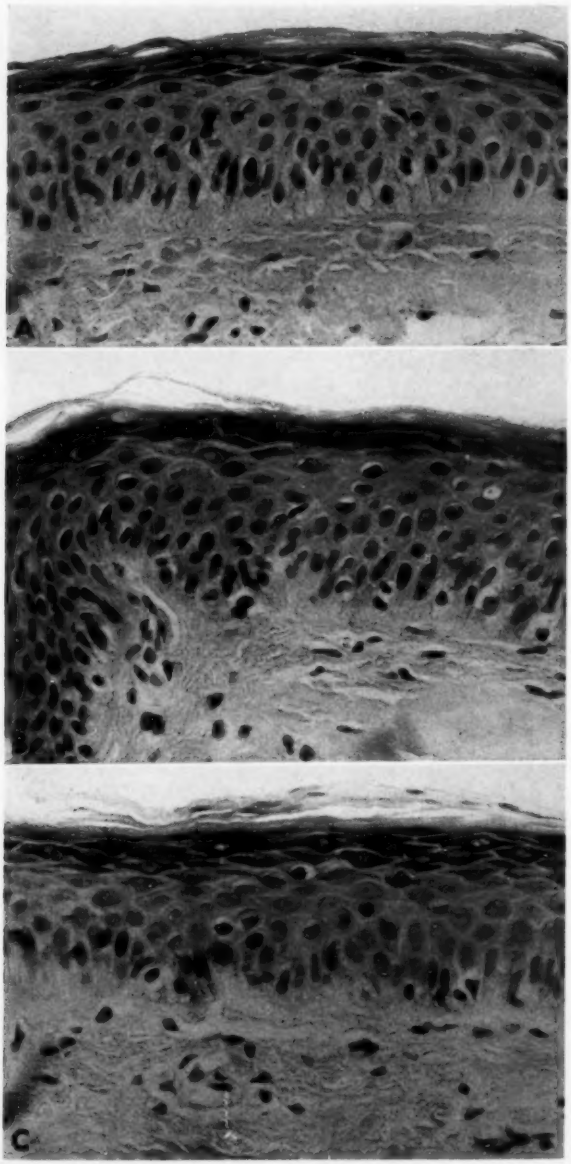

Fig. 112. Specimens of epidermis from the face of an elderly man. These show varying degrees of flattening of the rete ridges, and mild hyperkeratosis. *C*, Shows some parakeratosis. Hematoxylin-eosin. × 800.

considered these filaments to be mitochondria, intercellular fibrils, or tonofibrils just formed from mitochondria. Under the electron microscope, however, the filaments of Herxheimer have properties identical with those of tonofibrils. Laterally, the basal cells make contact with each other and with the spinous cells above them by way of intercellular bridges.

Between the basal cells are the dendritic melanocytes, or "clear cells" of Masson. These melanin-forming cells, which are ontogenetically related to the glial cells of Schwann, can be recognized in histologic sections by their small, darkly staining nucleus and their clear cytoplasm, which radiates into long processes, insinuated between the more basally located epidermal cells. Those melanocytes that contain melanin granules are easily recognized (Figs. 110, 111), but the cytoplasm of the nonmelanotic ones is clear, thus the designation "clear cells" by Masson. Impregnation of tissues with silver salts renders the pigment granules black, making the melanotic cells easy to recognize.

The cells in the various layers of the epidermis represent the converted elements of the germinative cells, the mission and fate of which are the formation of the dead stratum corneum. Together with the other authors, we regard this continuous formation and shedding of the stratum corneum as a holocrine type of secretion of the epidermis, in the same sense that the sebum is the secretion of the sebaceous gland.

The cells above the basal layer constitute the *stratum spinosum* or, in a strict sense, the true mucous layer of Malpighi (Figs. 110–113). This layer forms the greater bulk of the epidermis, which may reach a thickness of 0.2 mm. in regions other than the palms and soles, where it is even thicker. The spinous cells are the first direct product of the basal cells and represent a morphologic and functional variant of a single cell type. Normally, daughter cells from the basal cells move up and are transformed into spinous cells. These are heaped into several irregular layers, disposed in a mosaic pattern. The size, shape and structure of these cells become progressively different as the cells move away from the basal layer. Ascending from the deeper layers, the cells are polyhedral, globose, and then gradually flattened and parallel to the surface. The nuclei of the spinous cells become less stainable as the cells move toward the surface. Occasionally, some of the more basal spinous cells are in mitosis, suggesting that they have not lost the ability to divide and that they contribute at least in part to the maintenance of the spinous layer. It is not always possible, however, to ascertain whether these are spinous cells or basal cells which have been squeezed out of the way. The cells of the spinous layer have conspicuous intercellular bridges visible in good preparations, even in sections stained with hematoxylin and eosin (Fig. 113). Be-

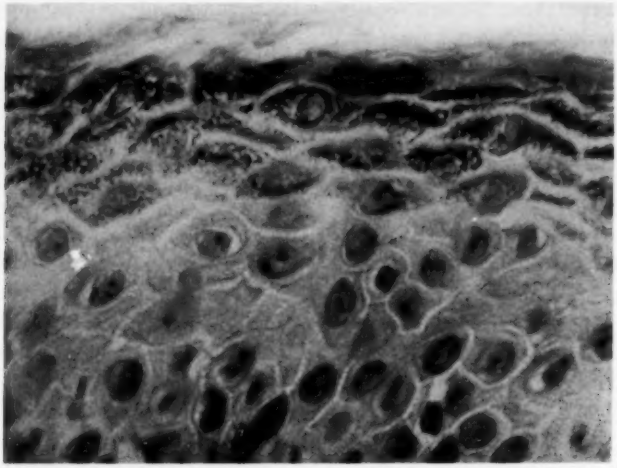

Fig. 113. Skin of the face of a man. Note the well formed granular layer, and intercellular bridges in the prickle cell layer. Hematoxylin-eosin. × 1500.

tween the intercellular bridges are spaces or canaliculi, which function as lymphatic channels through which seep the nutritive substances derived from the dermal vessels, the epidermis itself being avascular.

Delicate cytoplasmic striations, the tonofibrils, which can be seen in all epidermal cells, are particularly clear in the cells of the spinous layer. Tonofibrils have a certain direction and orientation in the cytoplasm and are apparently attached to the desmosomes.

Above the stratum spinosum, and somewhat blending with it, is the *stratum granulosum*. This layer varies in thickness according to the particular region of the body, but it is about four cells thick (Figs. 112, 113). The granular cells are variably flattened; their nuclei, often misshapen, stain lightly or not at all. The cytoplasm contains different numbers of highly chromophilic particles of various sizes and shapes, the keratohyalin granules of Unna. Although the exact nature of these granules is not definitely known, they contain calcium, but no deoxyribonucleic acid, and neither -SH nor -S-S- groups. The electron microscope indicates that keratohyalin granules are cell products that form part of the final composition of keratin in the corneal layer. The epidermis of mucous surfaces has no stratum granulosum. Some alterations in keratinogenesis may cause a disappearance of the granular layer. In those places where keratinization is apparently slowed down, the granular layer may become strikingly thicker.

In the palms and soles the epidermis has a *stratum lucidum* above the stratum granulosum. It is three or more cells thick, and the cells

are flattened, hyalin, very poorly chromophilic, apparently anucleated and oriented parallel to the surface of the skin. This layer is said to contain "eleidin," an allegedly sudanophilic substance said to be derived from the keratohyalin granules. Actually, no one knows what eleidin is. Outside of friction areas, the epidermis seldom reveals a stratum lucidum. The stratum lucidum and the stratum granulosum together constitute the so-called transitional layer of the epidermis. This layer seems to play an essential role in the protection of skin against the penetration of extraneous substances from the outside and against the loss of liquids from the inside.

In histologic preparations the *stratum corneum* seems to consist of 5 to 10 layers of flattened, keratinized, non-nucleated dead cells, which stain homogeneously with acid dyes (Fig. 112). Those who have stripped the successive layers of the stratum corneum with Scotch tape, however, know that the number of layers that can be removed is considerably larger than 10, and may, in fact, vary from 20 to 30 or even more, depending upon the region studied. The superficial cells of the stratum corneum are constantly being desquamated and form the stratum disjunctum of Ranvier; the cells in the deeper part are more firmly cemented together and are not easily desquamated. In those surfaces of the body, such as the palms and soles, which are subjected to pressure, or to various stresses, the stratum corneum is much thicker than it is elsewhere and may be 50 per cent or more of the total thickness of the epidermis. The corneal cells, normally poor in water content, have a notable capacity to absorb water. The low water content of the stratum corneum must contribute to the dry appearance of the surface. The presence of lipids, together with hydrophilic lipid esters, could help prevent the loss of water from the skin by emulsification. Mucous or pseudomucous surfaces normally have no stratum corneum.

THE DERMOEPIDERMAL JUNCTION

When the epidermis is separated from the dermis by enzymatic digestion or by acid hydrolysis, and its under side studied, it can be verified that the epidermal ridges or "rete pegs" seen in histologic sections are cuts through anastomosing ridges of different sizes, between which are found depressions and pits. There are characteristic regional differences in the architecture of these epidermal ridges, which are related to the arrangement of hairs and sudoriferous glands. The epidermal ridges radiate from the pilary canals toward the ducts of sweat glands. In some regions the ridges may be arranged concentrically around these structures. The under side of the epidermis is well developed in glabrous or nearly glabrous surfaces. The palmar and plantar surfaces,

the lips, the labia minora, the glans penis, and other areas, which are altogether glabrous, have superlatively developed, elaborate epidermal ridges. The surfaces of contact between the epidermis and dermis, being interlocked, bear a negative imprint of each other. During old age the ridges on the under side of the epidermis gradually flatten out, and in senile skin they are often completely obliterated.

As we have mentioned earlier, numerous, delicate cytoplasmic denticles from the cells of the basal layer grow into the surface of the papillary body, providing a close intimacy of dermis and epidermis. The cytoplasm of epidermal cells is not directly in contact with the dermis, however; a basement or basal membrane separates even the delicate cytoplasmic processes of the basal cells from the dermis.

Much has been written about the basement membrane of the epidermis.[4] Briefly, in histologic preparations the basement membrane appears to be a matting of reticular and delicate elastic fibers. It stains well with the PAS (periodic acid Schiff) techniques. Under the electron microscope the true basal membrane is a band about 350 angstroms thick that follows every contour of the epidermal cells, being separated from them by a "space" 300 angstroms wide. All metabolic exchange between the capillaries in the dermis and the cells of the epidermis must pass through this membrane.

The dermoepidermal junction, though genetically determined, is morphologically adapted to the normal stresses to which the skin is exposed. In the palms and soles the basal cytoplasmic processes of the epidermal cells are long and the development of a histologically demonstrable basement membrane is extensive. The epidermal ridges attain a greater depth and complexity in these areas than elsewhere. The epidermal ridges in the abdomen or in the medial surface of the thigh are shallower and the basal cytoplasmic processes are less visible.

THE INTERCELLULAR BRIDGES AND TONOFIBRILS

Adjacent epidermal cells do not form complete adhesion. Contact is made at numerous small areas, the intercellular bridges that are separated by spaces or canals. Intercellular bridges are best defined in the stratum spinosum; they gradually become less distinct in the stratum granulosum, and seem to disappear in the stratum corneum. About midway in each intercellular bridge is a spindle-shaped node of Bizzozero, or desmosome. Bridges and desmosomes are seen best in the epidermis of the palms and soles. In order to explain, even briefly, the intimate structure of the desmosomes, it is necessary to describe their relation to the tonofibrils, delicate cytoplasmic striations seen in all cells of the epidermis. These striations, distinct in the spinous cells, are less clear in the stratum granulosum and seem to

disappear in the stratum corneum. In the cytoplasm are masses of fine filaments, the tonofilaments, about 60 angstroms thick; when matted together, these could form the tonofibrils seen in histologic preparations. The desmosomes, or points of contact between two intercellular bridges, under the electron microscope, seem to consist of the thickening of the plasma membrane of both cells, and tufts of fibrous material are directed toward them from the interior of the cells. Several layers of different densities are symmetrically arranged on either side of the intercellular contact layers. Tonofibrils from the center of the cell go toward the plaques and become attached to them. Desmosomes are inconspicuous in the stratum corneum, but they are there and have been demonstrated with the electron microscope.

The basal cells of thin epidermis have few tonofilaments, but those of thick epidermis have more of them, and they are organized into fibrils. When thick bundles of filaments are directed toward the dermoepidermal junction, they could form the Herxheimer fibers mentioned earlier. Since tonofibrils are present in basal cells and the fibrils contain alpha proteins, keratin formation begins in the basal layer. Tonofilaments are most numerous in the spinous cells. In the stratum granulosum some of the fibrils appear less electron dense and lack a filamentous structure, probably indicating a macromolecular rearrangement in the formation of prekeratin. In the stratum lucidum the structure of the fibrils is altered, but the fibrils terminate at the desmosomes as do those in the spinous cells. In the stratum corneum the tonofibrils are not usually clearly seen under the electron microscope, because the cell matrix in which they are embedded is as electron dense as the fibrils themselves are.

GLYCOGEN

Although the epithelium that lines mucous membranes nearly always contains demonstrable glycogen, the normal epidermis of man has relatively small amounts of it or none at all. Glycogen is found sporadically in restricted sites, and its presence is usually associated with certain special features. When present, glycogen is largely found in the cells of the upper spinous layer; rarely it may also be found in the cells of the lower layers. The epidermal cells around the orifices of the pilosebaceous canals and the ducts of sweat glands often contain traces of glycogen. Depressions or deep grooves in the skin, abrasions, lesions, and pilosebaceous orifices that enclose blocked cornified material are generally surrounded by altered epidermal cells that are variably rich in glycogen. Thus glycogen is present in the epidermis where the normal rate of keratinization seems to have been impaired. Since glycogen is not found in the epidermis with normal

keratinization and mitotic activity, its presence must signal some aberration in these processes. When epidermal cells are replete with it, glycogen is usually in the form of small granules aligned in rows.

In the thin epidermis of human fetuses younger than four months, the basal as well as peridermal layers are rich in glycogen, the cells of the periderm being particularly laden with it. In the fourth month, when the basal cells begin to given rise to the anlagen of the cutaneous appendages, glycogen disappears from these sites of rapid cell division, although it may remain in the upper layers. When keratinization begins, there is a sudden reduction in the content of glycogen in the epidermis, and it disappears altogether near term, when keratinization is in full swing.

In postnatal epidermis the storage of glycogen in the basal cells is inversely related to mitotic activity, and that in the stratum spinosum is related to an alteration in keratinization. Glycogen is also stored in the case of epidermal lesions that are accompanied by parakeratotic changes.

THE SURFACE LIPID MANTLE OF THE EPIDERMIS

The lipids on the surface of the skin come from the epidermal cells proper, from the secretion of sebaceous glands, and some probably from the secretion of sweat. Of these sources, the contribution from sweat glands must be of small consequence. Since stratum corneum in areas that are poor in sebaceous glands also contains appreciable lipid substances, these must be derived from a lipophanerosis of the epidermal cells during keratinization.

Surface lipids contain about one third free fatty acids and one third esterified fatty acids; these form a homologous series that range from short to long chains. The surface lipids also contain a mixture of unsaponifiable substances, normal-chain aliphatic alcohols and variable amounts of squalene. There are small amounts of vitamin E and appreciable quantities of acidic or phenolic compounds, which may serve as antioxidants; there are some glycerides and traces of phospholipids. The complex mixture of this lipid mantle is hydrophilic. Detailed accounts of the chemistry of surface lipids may be found in Rothman[8] and, among others, in Wheatly[15] and Nicolaides and Wells.[5]

There are notable regional differences in the composition of the surface lipids. Furthermore, changes also occur with aging. This aspect of the field is now being explored with thoroughness, and future finding should be illuminating to a better understanding of the skin of the infant, the child, the adult and the aged.

THE HISTOCHEMICALLY DEMONSTRABLE ENZYMES

With the continued systematic application of histochemical techniques to the skin, we are gradually accumulating valuable information of the enzyme systems present in the epidermis. Only a brief sketch of these findings will be given here; more detailed reviews have been compiled by Steigleder,[12] Serri,[9] Montagna and Ellis[3] and Montagna.[4] Let it be understood that although each of the enzymes listed below is found in the epidermis over the entire body, there are striking regional differences in the intensity of activity. Aging differences also occur, the various reactions being more intense in the epidermis of the child than in that of the adult, and stronger in that of young adults than in that of aged subjects. Skin, being exposed to the constant ravages of the environment, has at all times minor subclinical lesions, which also reveal various departures in enzyme concentrations. In order to appraise his findings intelligently, the investigator must be alert to all these variants.

Granules reactive for cytochrome oxidase are found in the cytoplasm of all viable cells of the malpighian layer. Enzyme reaction is concentrated in the more basal cells, including the germinative layer, and becomes extinct in the cells of the stratum granulosum. The localization of this enzyme parallels the distribution of mitochondria, which are known to contain cytochrome oxidase. Succinic dehydrogenase and monoamine oxidase have a distribution similar to that of cytochrome oxidase. The techniques for all these enzymes may be applied with good results for the demonstration of mitochondria in the epidermis, which are otherwise mischievously difficult to show with the standard classic methods. We stress that the epidermis at the border of the orifices of pilosebaceous complexes is always more strongly reactive than that a distance from it. Although some carbonic anhydrase activity has been demonstrated in the basal cells of the epidermis, the techniques used for demonstrating it have dubious specificity. We must, therefore, await a refinement of methods before an accurate appraisal of its presence is available.

The epidermis contains amylophosphorylase, localized primarily in the lower cells of the malpighian layer. This enzyme system is more active where the epidermis is thicker. Occasionally one encounters strongly reactive foci in an otherwise moderately reactive epidermis, perhaps indicating sites of disturbance, which are probably accompanied by an abnormal accumulation of glycogen. The presence of amylophosphorylase in the epidermis is characteristic of the skin of man and that of other primates; the epidermis of the many other mammals we have studied contains occasional traces of it. The

accumulation of all these enzymes is much more intense in the epidermis of the child than in that of the adult.

The malpighian layer contains aminopeptidase activity. Enzyme activity is stronger in the epidermis of the child than in that of the adult. It increases perceptibly in sites of injury or in pathologic lesions that are accompanied by alterations in keratinization.

Normally there is no nonspecific alkaline phosphatase activity; injured epidermis may show large quantities of it. It is likely that a thorough investigation of the spectrum of phosphatases may yield interesting results. Sulfatases should also be investigated, for they are indubitably involved in keratinization. There is abundant acid phosphatase activity in the epidermis. Enzyme reaction, scant in the lower cells of the malpighian layer, increases centrifugally and becomes intense in the stratum granulosum; even the stratum corneum may be strongly reactive. Phosphamidases have been shown in the granular layer, where the reaction seems to be associated with the keratohyalin granules. The technique for this enzyme, however, is not beyond criticism, and the results may be of little value.

The entire malpighian layer shows some reactivity for beta-glucuronidase. In good preparations the enzyme tends to be concentrated in the cells immediately above the granular layer. The entire malpighian layer is rich in esterases. The intensity of the reactions is dependent upon the techniques and substrates used. So much has been written about esterases that it must suffice here to state that a large spectrum of

Fig. 114. Skin of the back in a 15-weeks-old fetus. Numerous intraepidermal nerve fibrils are present. These fibrils represent the terminal portions of the subepidermal arcades. Deep in the presumptive hypoderm are seen large nerve trunks. Acetyltiocholinesterase (Koelle and Friedenwald, modified by Gomori). × 50.

esterase activity is localized in the epidermis, including the superficial layer of the stratum corneum. An esterase-rich band of cells, immediately above the stratum granulosum, is clearly delineated in the epidermis of the axilla and the scalp, but not as clearly seen in the thinner epidermis of the abdomen and the inner surface of the thigh.

Using the techniques for the demonstration of cholinesterases, it is possible to demonstrate extremely delicate intraepidermal nerve terminals. These are seen much more clearly in the epidermis of the fetus, where they are more numerous either actually or relatively (Fig. 114).[11]

-SH AND -S-S GROUPS AND KERATINIZATION

This complicated and abstruse subject does not lend itself gracefully to a brief discussion. We are forced, therefore, to elect only a few fragmentary highlights. More complete details must be sought elsewhere.[2, 4, 8, 13]

Histochemical techniques reveal in the malpighian layer a scant concentration of alcohol- and water-insoluble -SH groups homogeneously distributed throughout the malpighian layer. The cytoplasm of the granular cells is moderately reactive, but the keratohyalin granules show no reaction. The stratum corneum is also lightly reactive. A narrow band of partially keratinized cells above the stratum granulosum has a conspicuous concentration of -SH groups. This layer corresponds to a keratogenous zone. The epidermis of the palms and soles, which has a generally stronger reaction throughout, does not have such a clearly outlined keratogenous zone, and the stratum lucidum is not comparable to the keratogenous zone.

The histochemical distribution of -S-S groups is similar to that of -SH groups, except in the stratum corneum, where -S-S groups are intensely concentrated. The keratohyalin granules in the stratum granulosum are singularly free of -S-S- groups.

The greatest volume of keratinizing epidermal cells consists of tonofibrils and keratohyalin granules, both of which must be considered to be equally involved in the formation of keratin. Keratohyalin granules do not undergo fibrillar transformation, but ultimately become dissociated and mixed with the fibrous content of keratinizing cells, dispersed between the fibrils. The fibrillar component of keratin, formed from tonofibrils, is rich in sulfur, whereas the perifibrillar substance, containing substances from the keratohyalin granules, is poor in sulfur.

The loss of fluids is an essential step in the final stages of keratinization. The dehydration of keratinizing cells, however, begins deep in the stratum corneum, where normally hydrated cells are also present;

dehydration then, cannot be simply due to an evaporation of water. The loss of fluid at this level, therefore, is probably caused by a release of the bound water molecules from proteins. In the higher levels of the stratum corneum, evaporation of water could lead to a complete consolidation of the keratin.[2]

Although the histologist finds it convenient to speak of a keratogenous zone in the epidermis, such a designation is inaccurate. The results of histochemistry, electron microscopy, x-ray diffraction patterns, and chemical analyses show similarities in the contents of the malpighian layer and those of the corneal layer. The cells of the malpighian layer also contain the basic proteins of keratin. These proteins could gradually reorient themselves within the spinous cells in such a way as to become precipitated into tonofilaments and tonofibrils. Keratinization, then, is a continuous process that begins as soon as the cells leave the germinative layer and is concluded with the dehydration of the cells in the upper part of the corneal layer.

THE PIGMENTARY SYSTEM

The dendritic pigments producing melanocytes in the epidermis are "inquilines" of the epidermis. They are argentophilic or aurophilic, characteristic features that they share with the elements of the nervous system, to which they are related. Melanocytes elaborate melanin granules and disperse them to the surrounding epidermal cells (Figs. 111, 115). Neither the mechanism by which the melanin granules are

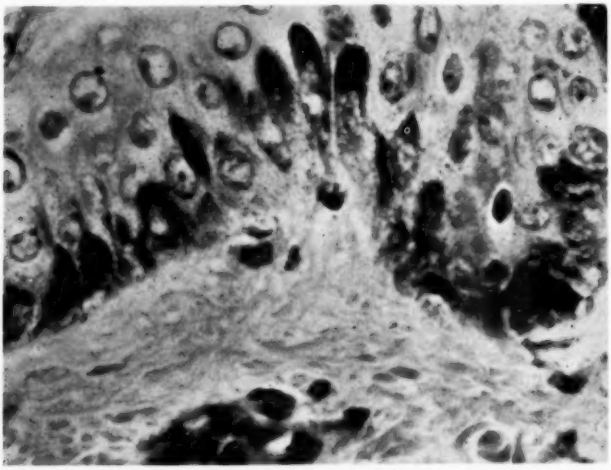

Fig. 115. Skin of the face in an adult Negro. All the cells of the basal layer are loaded with pigment. Hematoxylin-eosin. × 1500.

initiated within the melanocytes, nor that by which the cells transmit them to epidermal cells is known.

The color of skin is dependent less upon the number of melanocytes than on the amount of pigment they produce. Even the differences in skin color between the races are due to functional variations rather than to the number of melanocytes present. There are great regional variations in the melanocyte system in the same person. For example, one of every 10 cells in the basal layer of the appendages is a melanocyte, whereas on the cheek there is about one in every four. The number of melanocytes in a given area is related to their size and shape. In areas that contain more than 1000 per square millimeter the melanocytes are small and have short dendrites; in areas where the number is less than 1000 per square millimeter the melanocytes are larger and have longer dendrites. There is an appreciable reduction in the number of epidermal melanocytes with aging.

The shape, size and distribution of melanocytes is under genetic control. Also, internal factors must play a role in the number of melanocytes present: the population of melanocytes in the regenerated epidermis of scars may be smaller than that of normal skin, but it is near that of the normal number. Solar radiation, which activates melanogenic activity, has no effect upon the number of melanocytes. Melanogenesis is also controlled by hormones; cortical steroids slow it down, melanocyte-stimulating hormones increase it, and "melatonin" inhibits it.

Like the epidermal cells around them, melanocytes are ultimately desquamated upon the surface of the skin. This means that melanocytes are a self-perpetuating system of cells.

Melanocytes may be active, melanotic, or inactive, amelanotic. When active, they can be demonstrated electively by their specific affinity to "dopa," 1-3, 4-dihydroxyphenylalanine, a substrate which, when acted upon by the tyrosinase in the melanocyte, forms the black pigment "dopa quinone." Amelanotic melanocytes are dopa-negative, but can be demonstrated with methylene blue. The formed melanin granules can be made more visible with gold or silver impregnation techniques.

MITOTIC ACTIVITY

In spite of some disagreement, cell division in the epidermis occurs chiefly in the basal layer (Fig. 116). In making this statement, we do not deny that some of the cells immediately above the basal layer undergo mitosis. Even admitting this, let one be cautioned against too ready an acceptance of these as "spinous cells." Remembering that the under side of the epidermis is enormously uneven, thrown into folds and ridges, and pock-marked by pits and craters, cells that in

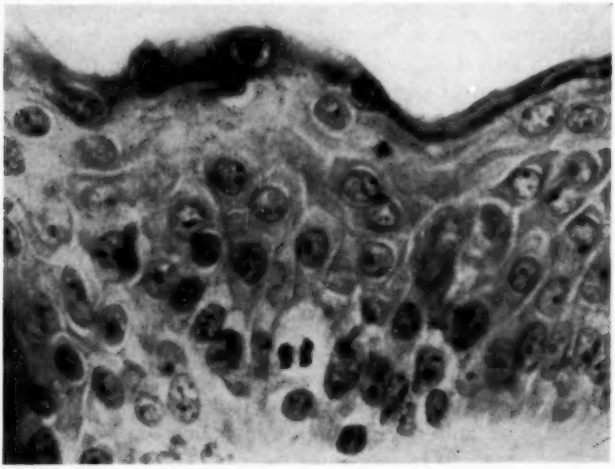

Fig. 116. Skin of the face in an adult. A cell in the basal layer is in metaphase. Hematoxylin-eosin. × 1500.

one histologic plane seem to be spinous cells may be spaced in the basal layer in another level. Notwithstanding these objections, it would be unrealistic not to admit that cells in the spinous layer of the deep epidermal ridges in the palms and soles undergo division, for indeed they do.

The histologist has long puzzled over the problem of the apparent insufficiency of mitosis in the epidermis to replace the cells lost at the surface. That the number of mitotic figures is adequate is amply demonstrated by the fact that the stratum corneum is normally never depleted and remains the same thickness under normal wear and tear. When more of the stratum corneum is experimentally removed, there is an increase in mitotic activity comparable to the amount of the layer removed.[6]

Most of the information we gathered on the requirements of mitotic activity in the epidermis has been obtained from the skin of the mouse. It is not the place here to treat this complicated subject. It is pertinent, however, to mention that epidermal mitotic activity in rodents follows patterns of diurnal cycles related to the periods of activity and rest. During the periods of bodily activity, epidermal mitosis is low, but during rest and sleep it is high. This is probably related to the levels of circulating blood sugars. Sex hormones, nutrition, bodily activity, stress, age and a number of other factors all have profound influence on the rate of epidermal mitotic activity in mice. Information on mitosis in the epidermis of man is scant. We have here

perhaps the largest gap in our knowledge of the biology of the epidermis. Those who wish a more complete review of the mitotic activity in the epidermis are referred to Montagna.[4]

GENERAL CONSIDERATIONS

The epidermis is an exceedingly restless tissue. This restlessness, apparent instability, modulatory tendency and sensitiveness to environmental changes are a part of its biological template and wisdom in adapting constantly to environmental changes within and without. The epidermis achieves stability from its inherent instability.

Every structural and functional feature of the epidermis is aimed at the completion of an effective protective barrier in the stratum corneum. Studies of this dead, but far from inert, structure are revealing daily the particular loving care with which it is fashioned. Every detail of this structure, the rates of wear and tear, its physical and chemical properties are tailored to keep agents of all sorts from penetrating the skin.

Studies of electrical conductivity in the epidermis have shown in the lower part of the stratum an electronegatively charged field, which is believed to repel anions and to prevent cations from penetrating further. This field would be the physical and physiologic barrier of the epidermis and has been designated the "barrier layer."[14] The epidermis has a low electrical conductivity when the barrier layer is intact and a high conductivity when the barrier is broken or injured.[1]

The surface of the epidermis is coated with a layer of lipids and organic salts liberated from the keratinizing cells and from the sebum and sweat. This complex varnish, called the "acid mantle" because it has a pH of 4.5 to 6.0, is believed to have antifungal and antibacterial properties. Perhaps in addition to the substances within the acid mantle, the epidermis itself may have properties that are noxious to potential invading microorganisms.

These and other properties of the stratum corneum focus attention upon the delicate and subtle design of the process of keratinization. The orderly process of the syntheses of sulfur-bound polypeptide chains is accompanied by ancillary processes all aimed at making skin an effective barrier and an organ whose many other properties will surely, in time, be unveiled.

CONCLUSIONS

Rather than a conclusion, we believe that the brief sketch we have presented on the biological properties of the epidermis needs to be pointed up. Thus the reader who is unaware of the enormity of its

importance may leave with certain basic generalizations. Even though the kernels of our understanding of the anatomy, biology, and chemical and physical properties of the epidermis have not changed appreciably from those found in textbooks, current basic research has given us a much better comprehension of fine structure of the epidermis, of its metabolic activities, of its function as a barrier against noxious external stimuli and against the loss of water from the inside, and finally of the essential process of keratinization and melanogenesis.

It is strange that so little progress should be made toward a better understanding of the skin of the fetus. We still do not know the exact chronology of its morphologic modification and, even more important, the functional modifications of the epidermis during fetal life. This is the aim of our research now in progress. We are convinced that by beginning with a thorough understanding of the morphogenetic events, we shall in time come to a better understanding of the skin in postnatal life.

The salient features of the structure and function of the epidermis may be thus summarized:

1. More than other cutaneous structures, the vital cells of the epidermis demonstrate a notable capacity to assume structure and function different from those which they normally assume. This is modulation. The epidermis has superlative regenerative powers; it has a metabolic activity of variable intensity, which depends upon particular functional states and upon the site being examined. This metabolic activity is related specifically toward the reproduction of cells injured or lost by lesions; toward the transformation of the germinative cells into cornified ones (keratinization); toward the formation of melanin by melanocytes, a third aim of the total activity of the epidermis.

2. Interposed between the external and internal environments, the epidermis is sensitive to the variations of both. This sensitivity may be brought about by the highly developed epidermal enzymatic system, which probably presides over the regulation of metabolism. Having no blood vessels of its own, and provided only with free nerve endings, the vitality and integrity of the epidermis must depend largely upon the integrity and functional state of the dermis. Nutritive and other essential substances from the dermis probably seep through the intercellular spaces. Increasing evidence points toward the dermis as the tissue which plays the role of maintaining the unity of the epidermis and in guiding the differentiation of its cells.

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